



CANCER





# **CANCER**

## **Diagnosis, Treatment, and Prognosis**

*by*

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**With 745 text illustrations and  
42 color reproductions**

St. Louis  
**THE C. V. MOSBY COMPANY**  
1947

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Reprinted January 1948  
Reprinted September 1948

Printed in the  
United States of America

*Press of  
The C V Mosby Company  
St Louis*

This book is respectfully dedicated  
to  
Henri Coutard MD  
and  
Arthur Purdy Stout MD



## PREFACE

This book is not an encyclopedic dissertation of all knowledge of cancer. Our purpose is to provide a text which will facilitate the acquisition of general information and serve as a guide toward richer sources of knowledge of cancer. The clinician and the student of cancer often need information on the treatment and prognosis of the disease which is not available in the treatises on pathology or which, when found there, is admittedly too condensed or antiquated. The numerous chapters, books and articles devoted to the treatment of cancer often start upon the assumption that a correct diagnosis has already been established, thus seldom providing details of the clinical evolution and of the differential diagnosis which are most useful to the nonspecialized worker. To present an integrated view of all these aspects is what is here intended.

The first part of this book is dedicated to subjects of general interest and application in the field of malignant neoplasms. We are privileged in presenting a chapter on Cancer Research especially contributed by Dr Michael B Shumkin, of the staff of the National Cancer Institute, who is eminently suited to write this review. The chapter on Surgery of Cancer was graciously edited by Dr Eugene Bricker, Associate Professor of Surgery at Washington University School of Medicine and former chief surgeon of the Ellis Fischel State Cancer Hospital. The chapters on Pathology of Cancer and Radiotherapy of Cancer complete the first section of the book.

The second part of this book is divided according to systems and subdivided as necessary according to anatomy or pathology. The word *cancer* at the heading of any chapter indicates that malignant tumors of different origin are included, *carcinoma* is used as a heading when only malignant epithelial neoplasms are considered, and the rarer tumors of the same area are treated in the section of differential diagnosis, finally, the word *tumor* has been chosen as a heading whenever the frequency or the seriousness of the benign tumors, the difficulties of differential diagnosis of benign and malignant tumors or whenever the importance of the treatment which is indicated in either case justify a joint consideration.

The length of some chapters of this book is neither commensurate with the importance of the subject nor with the incidence of the tumor under consideration. This disparity has been deliberate, for we have been guided rather by the desirability of information in certain rare subjects and by the necessity of greater knowledge on some aspects of the more curable forms of cancer. Important recent developments have also received priority on space.

Each chapter, section, or subsection of the second part of the book follows the same outline under the following headings: Anatomy, Incidence and Etiology, Pathology, Clinical Evolution, Diagnosis, Treatment, and Prognosis. The order of the illustrations follows the arrangement of these subheadings.

Under the heading of Anatomy, a short description of the organ or region is given with emphasis on any pertinent details, but frequently this description

is incomplete from a purely anatomic point of view. Under this heading is featured a more detailed discussion of the *lymphatics* than is usually found in textbooks of anatomy because of their unquestionable importance in cancerology. The thorough monograph *Anatomie des lymphatiques de l'homme*, by Professor H. Rouvière of the University of Paris (Masson et Cie), and its English translation (Edwards Brothers, Inc., 1938) have been consulted often in the elaboration of these summaries.

Incidence and Etiology comprise whatever relevant information has been gathered on these subjects, but these data are purposely short to avoid repetitions and academic discussions.

Under the heading of Pathology, special attention has been given to the *gross pathology* because of its importance to the clinician as well as to the surgeon and the radiotherapist, the *metastatic spread* of malignant tumors and the manner and frequency of this spread have been given special consideration. In general, the *microscopic pathology* is deliberately brief except when emphasis is deemed necessary.

We believe that a knowledge of the Clinical Evolution of cancer is of cardinal importance. Under this heading we have given details of the relationship of symptoms to lesions which should help clarify the expected course of the disease and facilitate earlier diagnosis.

Under Diagnosis are outlined the pertinent factors and required examinations which lead to the recognition and identification of the tumor in question. A section of *differential diagnosis* presents the pathologic entities which most frequently offer a problem of diagnosis. Rare tumors not justifying a special chapter have been detailed when they are considered in the differential diagnosis of other tumors.

Under the heading of Treatment we have avoided details of therapeutic techniques which are of interest only to the informed specialists, the treatments which may be considered are discussed and the treatment of choice is stressed. Our general interest in the cancer problem should be sufficient safeguard against suspicion of bias, but our choice is likely to be disputed. The introduction of new techniques or progress in the application of present ones, however, may cause a revision of these opinions.

An effort has been made to offer an idea of the Prognosis based mostly on statistics of results, thus, we believe, is greatly needed since in many instances the general practitioner has been too much impressed with the hopelessness of certain forms of cancer and is unaware of the relatively great possibilities of adequate treatment. Only serious, well-controlled statistics, preferably of patients followed at least five years, are quoted.

At the end of each section will be found a list of References. A considerably greater number of references were consulted than are listed but we have presented only the works which are quoted in the text. These references provide a source for further information or indicate the author or authors to whom credit is due.

The text is accompanied by 76 tables and 745 figures, including clinical photographs, photographs of gross specimens, photomicrographs, and drawings. The quality of most drawings, which greatly enhance and clarify the written

word, is a credit to Virginia Starz Ackerman, to whom we were pleased to intrust this delicate role. The clarity of the photomicrographs and many of the photographs is the result of the technical ability of Mr. J. F. Barham. Nine full page color plates complete the illustrations.

This book could not have been written without the unselfish help of many of our friends, some of whom are credited with the illustrations which they graciously contributed. Dr. Hamilton B. G. Robinson, Professor of Oral Pathology, Ohio State University, is responsible for most of the information contained in the section on Tumors of the Lower Jaw. Dr. David V. LeMone has been of invaluable help in the redaction and illustration of the chapter on Bone Tumors. He has also given much needed advice concerning diagnostic roentgenology throughout the book and contributed several of the roentgenograms. From Washington University School of Medicine, Dr. Thomas Burford gave needed advice for the clarification of treatment of thoracic tumors, and Dr. Carl V. Moore and Dr. Edward Reinhard made valuable suggestions for the chapter on Leucemias. To all those mentioned and to our teachers and associates, all of whom naturally have moulded the authors' opinions, an expression of gratitude is sincerely extended.

The unselfish cooperation of Mrs. Elizabeth Cooper of the University of Missouri Medical Library, and of Miss Marion A. Murphy, of Washington University Medical Library, has been paramount in providing the authors with wide and prompt access to the medical literature, without their valuable help our difficulties would have been much greater.

We want to thank the members of the Missouri State Cancer Commission and its executive secretary, Mr. Richard J. Connor, for the facilities opened to ourselves and our secretary for the realization of this work. All workers of the Ellis Fischel State Cancer Hospital have in one way or another, knowingly or unsuspectingly, contributed to this book, their anonymous task deserves great credit, we are pleased to recognize Miss Shon Lockhart and Mr. Leo Schmitt for their loyalty.

We owe a special word of thanks to Miss Lura Nagel, our secretary, whose cooperation, loyalty, and thoroughness have been definite assets in our undertaking and to Mrs. Elizabeth I. Ackerman for her repeated revisions of the manuscript, her efforts toward the improvement of the text and her kind interest in our work.

*Lawrence V. Ackerman*

*de Legato*





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# Part I

## Chapter I

### INTRODUCTION

The importance of cancer as a disease threatening humanity need not be overemphasized. In the United States, cancer is one of the major causes of death, second only to diseases of the heart, kidney, and circulatory system. In 1940 there were 170,000 deaths from cancer in the United States (*Vital Statistics*), and it is estimated that if the present trend continues there will be 200,000 deaths from cancer in the year 1950.

Admittedly, death statistics are not very accurate, for the diagnosis on a death certificate is usually based on clinical assumption and seldom on confirmed pathologic findings. In general, however, it is admitted that cancer is underdiagnosed rather than overdiagnosed. The progressive increase in the number of reported deaths from cancer is, to a large extent, only apparent, for more cases are being diagnosed accurately as the medical profession becomes cancer conscious. The greater mortality from cancer is also due to an increase in the numbers of individuals reaching advanced age. For instance, in the State of Connecticut there were 14 times as many deaths from cancer in 1940 as in 1930, but there were also 17 times as many individuals 40 years of age or older in 1940 than in 1930 (MacDonald). In this respect it is estimated that in 1940 there were in the United States 9,000,000 individuals 65 years of age or over and that this group can be expected to increase to 22,000,000 by the year 1980. In view of the fact that cancer is prevalent among individuals of this age group, its frequency may continue to increase in the United States for a number of years on the basis of these facts alone. In addition, there seems to be a true increased incidence in certain forms of cancer, such as carcinoma of the lung.

Mortality statistics, however, in addition to their inaccuracy, are not the proper measure of the cancer problem. Some forms of the disease, such as cancer of the skin although very frequent seldom terminate in death, while other much less common forms such as carcinoma of the esophagus, are almost always fatal. Consequently, a study of the mortality rates does not give a correct idea of the distribution of cancer in the human body nor an adequate appraisal of the results of improved diagnosis and treatment. The distribution of tumors compiled from hospital records can be very biased. One hospital may receive a disproportionate number of patients with cancer of a certain organ because of the outstanding work of some members of its staff. Due to the difficulties in diagnosis, many cases of cancer of the lung may be seen in a tuberculosis sanatorium. The differences in the racial population of different cities as compared with rural areas and the differences of the age dis-

tribution in certain areas may considerably alter the apparent incidence of the various forms of cancer (Little)

In the State of New York, Levin has made a very creditable attempt to determine the number of new cases of cancer which occur each year in the various age groups. It is estimated that about 90 per cent of all cases are recorded. According to Levin, about 218 4 new cases of cancer can be expected per 100,000 of the population. The true figure is perhaps higher than this. The comparison of the number of new cases with the number of deaths

**CANCER**  
**AVERAGE ANNUAL INCIDENCE RATES PER 100,000 POPULATION**  
**NEW YORK STATE, EXCLUSIVE OF NEW YORK CITY**  
**1942-1943-1944**

ORDER OF INCIDENCE	SITE	SEX	ANNUAL INCIDENCE
1	BREAST	Female	80
2	CERVIX UTERI	Female	34 3
3	SKIN	Male	29 2
4	STOMACH	Male	27 1
5	COLON	Female	24 4
6	PROSTATE	Male	23 2
7	SKIN	Female	19 8
8	COLON	Male	19 6
9	STOMACH	Female	17 6
10	RECTUM & RECTOSIGMOID	Male	15 2
11	LUNG	Male	14 7
12	OVARY	Female	12 2
13	RECTUM & RECTOSIGMOID	Female	12 1
14	FUNDUS UTERI	Female	11 9
15	BLADDER	Male	11 5
16	LIP	Male	6 8
17	LEUKEMIA	Male	6 3
18	PANCREAS	Male	5 7
19	LIVER	Female	5 5
20	BLADDER	Female	5 2

ALL SITES FEMALE-270 8

ALL SITES MALE-231 8

Fig 1—In New York State carcinoma of the breast and of the cervix lead in incidence. Carcinoma of the skin is third. Note that cancer in the female surpasses cancer in the male by a considerable margin. (Courtesy of Dr. Morton L. Levin, State of New York Department of Health, Division of Cancer Control, Albany, N. Y.)

from a given form of cancer and also the appraisal of the number of patients living for each death due to cancer is helpful in evaluating not only the frequency of various types of cancer, but also their curability. According to Levin, there are 30 living patients with carcinoma of the skin for every death caused by this form of cancer, whereas there are only 13 living patients with carcinoma of the stomach for every death due to that tumor. It is also of great clinical interest to know the particular type of tumor which may be expected to develop in a group of male or female individuals at a particular

age Levin tabulated the prevalence of various types of cancer in males and females, using the figures of the State of New York (exclusive of New York City) According to his figures (see Tables I and II), testicular tumors are the most common malignant tumor in males between the ages of 25 and 29, carcinoma of the skin prevails between 30 and 54, carcinoma of the stomach most commonly develops between 55 and 69, and carcinoma of the prostate prevails between 70 and 84 years In females, carcinoma of the cervix is the

TABLE I MOST FREQUENT PRIMARY LOCATIONS OF CANCER IN MALES AT VARIOUS AGES

(Courtesy of Dr Morton Levin, Division of Cancer Control, Albany, N Y )

AGE IN YEARS	ORDER OF OCCURRENCE				
	1	2	3	4	5
0-4	Leucemia	Brain	Kidney	Eye	Adrenal
5-9	Leucemia	Brain	Hodgkin's	Kidney	Rectum
10-14	Brain	Bones	Hodgkin's	Mouth	Colon
15-19	Brain	Leucemia	Hodgkin's	Bones	Skin
20-24	Leucemia	Hodgkin's	Brain	Testis	Skin
25-29	Testis	Brain	Leucemia	Hodgkin's	Skin
30-34	Skin	Testis Colon	Brain Leucemia Hodgkin's	Rectum Stomach	Lung Lip
35-39	Skin	Colon	Brain	Stomach Lung	Testis Leucemia Hodgkin's
40-44	Skin	Lung Colon	Stomach	Brain Lip	Rectum Bladder
45-49	Skin	Lung	Colon Stomach	Brain Bladder Rectum	Leucemia Lip
50-54	Skin	Stomach Lung	Colon	Rectum Bladder	Brain
55-59	Stomach	Skin	Lung	Colon	Rectum Prostate Bladder
60-64	Stomach	Skin	Colon	Lung	Prostate
65-69	Stomach	Prostate	Skin	Colon	Rectum Lung
70-74	Prostate	Stomach	Skin	Colon	Rectum Bladder
75-79	Prostate	Skin	Stomach	Colon	Bladder Rectum
80-84	Prostate	Skin	Stomach	Colon	Bladder Rectum
85	Skin	Prostate	Stomach	Colon	Bladder Rectum



TABLE II MOST FREQUENT PRIMARY LOCATIONS OF CANCER IN FEMALES AT DIFFERENT AGES  
(Courtesy of Dr Morton Levin, Division of Cancer Control, Albany, N Y)

AGE IN YEARS	ORDER OF OCCURRENCE				
	1	2	3	4	5
0-4	Leucemia	Brain	Kidney	Eye	Bone Skin
5-9	Leucemia	Brain	Skin	Eye	----
10-14	Leucemia	Brain	Bone	Skin	Ovary Hodgkin's
15-19	Brain	Leucemia	Hodgkin's	Ovary	Skin Bones
20-24	Hodgkin's	Leucemia	Ovary	Skin	Breast
25-29	Breast	Cervix	Skin	Hodgkin's	Ovary Brain
30-34	Cervix	Breast	Ovary	Skin	Fundus uteri
35-39	Breast	Cervix	Ovary	Colon	Skin Fundus uteri
40-44	Breast	Cervix	Ovary	Colon	Skin Fundus uteri
45-49	Breast	Cervix	Colon	Ovary Fundus uteri	Skin
50-54	Breast	Cervix	Colon Fundus uteri	Ovary Skin	Rectum Stomach
55-59	Breast	Cervix	Colon Fundus uteri	Ovary Skin	Stomach Rectum
60-64	Breast	Cervix	Cervix	Fundus uteri	Skin Stomach
65-69	Breast	Colon	Stomach	Skin	Cervix Fundus uteri
70-74	Breast	Colon	Stomach	Skin	Cervix Fundus uteri
75-79	Breast	Colon	Stomach	Skin	Cervix Fundus uteri
80-84	Breast	Colon	Stomach	Skin	Rectum Fundus uteri
85+	Breast	Colon	Skin	Stomach	Liver

most frequent malignant tumor between the ages of 30 and 34, while carcinoma of the breast is the most common form of cancer after 35 years of age. Leucemia is prevalent in children of both sexes up to 9 years of age.

### DIAGNOSIS

The results of the treatment of cancer are unquestionably influenced by the time interval which elapses between the genesis of the lesion and its diag-

nosis For this delay the patient is too often blamed A large amount of money and considerable attention have been given to the education of the laity in an effort to incite patients to consult promptly There is no doubt that the general population should be educated as to the early signs and symptoms of cancer and that this education should be brought even to the high school students, as has been done in Michigan (Rector) and in Massachusetts (Lombard) But the education of the laity in cancer is limited by the general education of population groups and can improve only with the betterment of the standards of general education and general medical care The American Cancer Society has made a worth while effort to make the public conscious of the importance of early diagnosis However, an analysis of the records of any tumor clinic shows all too clearly that much of the time lost before diagnosis and adequate treatment is rather often due to the fact that the physician or physicians consulted did not suspect cancer, did not perform the indicated examinations, or were inadequately prepared to make the diagnosis In many instances, however only the insidious, treacherous character of the disease can be blamed for the delay in diagnosis and subsequent treatment

Unfortunately, physicians just leaving medical school are inadequately prepared for their role in the fight against cancer Regaud pointed out in 1928 that in general the instruction regarding malignant neoplasms was given in fragments, often without the necessary practical cohesion of this knowledge "The remedy to this situation," said Regaud, "is up to the Faculties of Medicine" Even today, the medical student acquires a disproportionate idea of the possibilities of treatment and is usually most impressed by the failures or by the incurability of some forms of cancer His education is superficial, partial and at any rate, inadequate for the role he should be able to fill Recently (1946) the National Advisory Cancer Council in the United States reached these conclusions "Even the better than average intern frequently lacks adequate understanding of malignant disease It is believed that the present undergraduate teaching of neoplastic disease both in time and content is not commensurate with the importance of the disease which now ranks second as a cause of death in this country Comprehensive courses are highly desirable This would avoid some of the repetition which now exists because the subject is taught in separate departments would provide ample time to cover the subject efficiently and would give the student a better integrated picture of the cancer problem" The training in cancer which the general physician should have must be given him either in his medical school or through channels easily accessible after he begins his practice This physician is in the most favorable position to help in the control of cancer, for he is the one who has the opportunity to discover cancer in its early stages (National Advisory Cancer Council)

Pathology laboratories to which physicians may submit specimens for microscopic diagnosis known as tissue diagnosis services, exist in fifteen states in this country Massachusetts and New York have established tissue diagnosis services and have made them free, regardless of the economic status of

TABLE II MOST FREQUENT PRIMARY LOCATIONS OF CANCER IN FEMALES AT DIFFERENT AGES

(Courtesy of Dr Morton Levin, Division of Cancer Control, Albany, N. Y.)

AGE IN YEARS	ORDER OF OCCURRENCE				
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40-44	Breast	Cervix	Ovary	Colon	Skin Fundus uteri
45-49	Breast	Cervix	Colon	Ovary Fundus uteri	Skin
50-54	Breast	Cervix	Colon Fundus uteri	Ovary Skin	Rectum Stomach
55-59	Breast	Cervix	Colon Fundus uteri	Ovary Skin	Stomach Rectum
60-64	Breast	Cervix	Cervix	Fundus uteri	Skin Stomach
65-69	Breast	Colon	Stomach	Skin	Cervix Fundus uteri
70-74	Breast	Colon	Stomach	Skin	Cervix Fundus uteri
75-79	Breast	Colon	Stomach	Skin	Cervix Fundus uteri
80-84	Breast	Colon	Stomach	Skin	Pectum Fundus uteri
85+	Breast	Colon	Skin	Stomach	Liver

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of whom the therapeutic results will greatly depend. In addition, the organization of therapeutic centers provides the best means for improving medical cancer knowledge which unquestionably results in earlier diagnosis and treatment.

### TREATMENT

If the prognosis of a patient with cancer depends in part upon the early diagnosis, the perfection of the treatment, whether it be surgical or radiotherapeutic, is decisive for cure or for death. "Surgeons and radiotherapists who undertake to treat curable cancers assume an exceptionally heavy responsibility because the unique stakes which they play are the life of the patient himself. If these thoughts constantly haunted, as they should, the spirits of those who occupy themselves with the treatment of cancer, the effort of organization of this branch of medicine should aim at the quality and power of the institutions and not at their number." (Regaud.) It is imperative that the fundamental choice of method and execution of treatment of patients with cancer be entrusted only to those who are adequately trained and qualified. With the advent of radiotherapeutic methods in the beginning of this century, it became more and more clear that a concerted effort was necessary in the fight against this disease and that such effort was better coordinated within special institutions. The Radium Institute of the University of Paris, The Radiumhemmet of Stockholm, the Memorial Hospital of New York, and others made the first efforts toward an appropriate organization of facilities and toward the training of workers in this field. In 1929, a special committee of the American Society for the Control of Cancer (Ewing, Greenough, and Geister) reported upon the question of therapeutic cancer centers as follows:

We have been forced to conclude that the treatment of many major forms of cancer can no longer be wisely entrusted to the unattached general physician or surgeon or to the general hospital as ordinarily equipped, but must be recognized as a specialty requiring special training, equipment, and experience in all aims of the service. We feel that the further development of cancer therapeutics will develop along the lines of concentration, organization, and specialization. It is well known that the most conspicuous progress in the treatment of cancer has always been accomplished by specialists. We recommend as an ideal, well within the possibility of accomplishment, the establishment of a limited number of cancer institutes. They should be located in large cities, be prepared to give the best modern treatment, and offer facilities for research and education.

To recognize this triple aim of treatment, research, and education is to recognize that cancer institutions be exceptionally well staffed. It would indeed be dangerous to entrust these responsibilities to amateur specialists or to those who have only an incidental or sentimental interest in the disease not only because the results of treatment would suffer considerably, but also because of the unquestionable danger of a spirit of defeat which they would spread among the members of the medical profession. The accumulation of clinical and pathologic data in such institutions creates the background for

training additional personnel. Thus the institutions fulfill not only a therapeutic service, but also the much broader service of educating and training specialists upon which the most immediate hope of cancer control depends.

*In establishing a cancer institute or hospital, the most important step is choosing the staff.* "The staff of the institute must be chosen with the realization that upon this selection alone depends the success or failure of the project, that neither the building nor the size of the endowment but the background, training, experience, spirit, imagination and idealism of the leaders and their associates will be the determining factors. The growth of the institute must be controlled and limited solely by its scientific contributions and accomplishments." (Cutler)

Statewide cancer control campaigns usually include the establishment of a series of small centers for diagnosis and treatment strategically placed throughout the territory. Although it is desirable to bring the diagnostic centers closer to the patients, a dissemination of therapeutic facilities requires equal dissemination of capable personnel which is not generally available. If such centers are created, they should be planned for the purpose of diagnosis and screening of patients and to assist in the post therapeutic follow up, at any rate their creation should never be contemplated in the absence, or to the detriment of a central institution (Regato). In an initial stage of cancer control it is preferable to finance the transportation of indigent patients from their home to the therapeutic center rather than to create multiple small centers where chances of a permanent cure will be extremely reduced.

The creation of cancer hospitals anywhere, by private institutions or by the state, should not be undertaken without securing the support and whole hearted cooperation of the state medical society. The medical profession has become appreciative of these cancer institutions, and experience shows a growing support from the medical profession toward them. The practitioner is grateful for the opportunity offered to him of further qualified investigation in suspected cases of malignant disease, and the patients realize that their recovery is often due to the acuity of their local physician. Occasional visits to special centers acquaint the practitioner with new developments and justly he comes to feel that he is also part of the institution.

In 1930, the Board of Regents of the American College of Surgeons, on the advice of its Committee on the Treatment of Malignant Diseases, announced a new policy. "The College is convinced that while awaiting further discovery of more efficient methods of treatment of the disease it is possible effectively to reduce the suffering and mortality from cancer by a recognized application of the knowledge that already is available. The merits of cancer institutes and cancer laboratories are fully acknowledged but it is felt that there is an urgent need for making our present knowledge more generally effective and that this need can be met most efficiently through the formation of cancer clinics in approved general hospitals." This policy of the American College of Surgeons has resulted in the formation of approximately 400 tumor clinics in the United States and Canada.

The purpose of these tumor clinics in general hospitals is to provide a workable system for close affiliation of the surgeon, pathologist, and radiotherapist, to provide for a more efficient service for the diagnosis, and to place the treatment of cancer in the hands of the most capable few. By the creation of a special cancer service in a general hospital, those members of the staff who are interested enough to devote their energies to cancer work can be brought into close cooperation with benefit to the patient, to the hospital, and to the scientific study of cancer. The American College of Surgeons has established a minimum standard for recognition of these clinics (Crowell). Unfortunately, in many instances, a minimum of interest or of capability is not available to fulfill the praiseworthy aims of a tumor clinic. Some tumor clinics have fallen far short of their duties because of the biased attitude of the members, which is most often due to the lack of proper knowledge and experience (Simmons).

Much has been said, though little has been written, about the proper qualifications for the ideal training of men who undertake to treat cancer. There is no question but that a skilled general surgeon may undertake the surgical removal of certain malignant tumors and that his background of general surgery is an asset in this undertaking. It is also true that general radiologists often have taught themselves the difficult art of radiotherapy of cancer and that their worth-while effort has contributed countless good results. There are also numerous examples of general pathologists who have excelled in the field of tumor pathology. But, generally speaking, there is little harmony when these men are obliged to work together. The finely integrated work of a tumor clinic or a cancer hospital may be the best example of scientific cooperation, when each member, regardless of his own discipline, has been trained in a background of cancer pathology, in an atmosphere of cancer research. It would consequently be desirable that men who undertake cancer work be trained in special institutions where surgeons would become acquainted with the rational possibilities and limitations of radiotherapy, where radiotherapists would look upon surgery as a necessary companion rather than as a competitor, and where the tumor pathologists would become acquainted with the clinical and therapeutic aspects of the disease besides its gross and microscopic appearance. "An isolated pathologist perpetuates his mistakes" (Stewart). This view is further reinforced by the fact that the greatest progress yet to be made in cancer control lies in the creation of a greater number of these specialists and in the realization that the undertaking of such training cannot be entrusted to men whose interest in cancer is only incidental. There is little incentive for the long training which is necessary in the different disciplines of cancer work, and for this reason the number of men who are actually trained lags far behind the requirements for these men in the future. The fellowships which were founded at the Memorial Hospital of New York by the Rockefeller Foundation in 1926 set a good example, and since 1937 the National Cancer Institute has devoted a great deal of attention to the selection and appointment of trainees in pathology and radiotherapy as well as in surgery of cancer. The National Cancer Institute Act, to which

ninety four of the ninety six members of the United States Senate attached their names, recognized cancer as a medico socio economic health problem (Spencer) The National Cancer Institute has become one of the outstanding centers of laboratory research in cancer, and through its Tumor Clinic in the United States Marine Hospital of Baltimore, has made its own attempt toward clinical research In addition the National Cancer Institute has distributed in recognized tumor clinics throughout the United States a total of 8 grams of radium which is held in loan for the treatment of cancer

## RESULTS

In order to permit a better appraisal of the results reported in medical literature, and through this to improve the character of these reports, it is important that the medical profession become acquainted with the frequent violations and errors of statistical rules in these reports (Cramer) "Papers which purport to decide the relative efficacy of different therapeutic procedures in the cancer field on the basis of statistics are often open to suspicion, especially when they deal with small numbers of patients, when the differences in reported cure rates are small, when there is reason to question the correctness of pathologic evaluation of material, and when the individual who reports the series is from the very nature of his professional accomplishment, not beyond the suspicion of bias (Stewart)

It is a fairly common practice to report the results of surgical treatment without mentioning the proportion of patients who were operated upon in relation to the number who were seen Obviously, the percentage of operability is an important factor in evaluating the final results In evaluating operative mortality, the percentage of operability must also be taken into account, for obviously the surgeon who undertakes the treatment of poor risk patients may have a greater operative mortality with perhaps a greater curability The same is true in reporting radiotherapeutic results For instance, the number of patients rejected for treatment of carcinoma of the cervix should be included so that the selection may be appraised It must also be taken into consideration that certain outstanding clinics, because of their very nature, receive a highly selective and consequently favorable group of patients

It has become standard practice in cancer centers to report five year results Admittedly, certain tumors such as carcinoma of the breast may recur after that period of years, but the five year results in most forms of cancer closely approximate the permanent results obtained Cases reported as followed from six months to ten years, for example cannot be given serious consideration for obviously many of the more recent cases may have recurred by the time the paper was published A new technique of treatment, surgical or radiotherapeutic, may warrant an early description not necessarily based on results In this case it would be preferable to eliminate statistics entirely in order to emphasize the aim of the publication

Another significant issue in the reporting of therapeutic results is the number of patients who are lost to follow up or who have died of intercurrent disease before the five year term period The Subcommittee on Radiotherapy



of Cancer of the League of Nations established the practice of including all these cases and considered them therapeutic failures. The resulting figures were unquestionably smaller than the actual results, but the procedure stimulated a greater effort in follow-up and eliminated unfair practices. In the United States such rules have seldom been followed, instead the patients lost to view or those dead of intercurrent disease before five years are usually considered an "indeterminate group" and are discounted in the final evaluation of percentage of results. This practice has been exaggerated to the point where some authors have included as many as 30 per cent of the total number of patients treated in this "indeterminate group" (Stewart). If an "indeterminate group" is eliminated it should never represent more than 10 per cent of the total number of treated cases. Obviously the results based on clinical diagnosis without benefit of biopsy cannot be considered for purposes of comparison.

## RESEARCH

The work of an institution devoted to the treatment of cancer cannot be divorced from cancer research. By cancer research is understood not only laboratory experimentation, but the clinical study of the disease, the constant improvement of the methods of treatment and the statistical research which this may imply. It is even desirable that laboratory research be carried out in therapeutic centers where the laboratory worker may become aware of the more immediate issues and of the relative importance of his work.

The States of New York, Massachusetts, Connecticut, Michigan and others have profited by the establishment of a division of cancer control usually under the Department of Public Health. Such divisions may undertake very profitable statistical research in respect to incidence, the actual need of facilities, coordination of work in different institutions, estimation of progress, and diffusion of information.

A reorganization of the American Cancer Society has resulted in a wider distribution and a greater number of grants for clinical and laboratory research in cancer.

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## Chapter II

### CANCER RESEARCH

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Experiences of every physician testify to the inadequacy of our therapy of neoplastic diseases. It is true that the early and full application of the existent methods of diagnosis and treatment can double the present rate of cures, but this would still leave a tragic residual in the death toll of over 170,000 per year. The conquest of malignant diseases awaits a greater understanding of the neoplastic process which can lead to more adequate means of prevention and treatment. This knowledge must be derived from the application of the experimental method to the problem.

Cancer research had its beginning approximately fifty years ago. More has been contributed to the knowledge of neoplastic diseases in this brief span than in all the preceding centuries, although the developments are not well recognized because few of them have reached the stage of clinical application. The final solution of the problem will probably come slowly through the gradual accumulation and integration of facts derived by the cooperative efforts of many investigators. Even the possible brilliant discovery of a single investigator will depend upon the sound foundation of previously established but less dramatic findings.

Public and professional interest in the cancer problem has gained steady momentum during the past thirty years. The efforts of the American Society for the Control of Cancer, supported by professional groups and public-spirited laymen, have made available ever-increasing funds. Research work in universities, hospitals, and other institutions has been assisted by several private foundations, of which the International Cancer Research Foundation, the Finney-Howell Research Foundation, the Anna Fuller Fund, and the Jane Coffin Childs Memorial Fund are devoted entirely to cancer research. The passage of the National Cancer Institute Act in 1937 mobilized Federal support of cancer research. At present approximately one million dollars per year are available for cancer research in this country. This support is scattered through thirty or more separate institutions throughout the United States. Of primary importance as separate institutes have been the National Cancer Institute, Bethesda, Maryland, the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, New York, the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine, and the Barnard Free Skin and Cancer Hospital, St. Louis, Missouri. Among the universities, Harvard, Yale, Columbia, Cornell, Wisconsin, and Minnesota have been leaders in developing

the experimental aspects of cancer. A great increase in the facilities personnel, and funds for cancer research is envisioned through the accelerated efforts of the American Cancer Society and through increased governmental appropriations at both Federal and State levels.

The number of publications dealing with the experimental aspects of cancer has been large and the number is continually increasing. A recent compilation lists over 12,000 references between 1900 and 1930. Two journals in the United States alone (*Cancer Research*, a continuation of the *American Journal of Cancer* and the *Journal of the National Cancer Institute*) are devoted exclusively to reports on cancer research. There has been a substantial increase in the number of reviews, monographs, and other attempts to synthesize the scattered information. It is hoped that the increasing use of statistical methods of examination of results to determine their significance and the new experimental methods becoming available for deeper examination of many problems in cancer will progressively increase the quality and the quantity of the work. In the writer's opinion, many of the apparent contradictions in the literature are due to the indiscriminate comparison of noncomparable data because of the belief that cancer represents a pathologic entity whereas it may be regarded more soundly as a group of diseases.

It is obviously impossible to survey the whole field of cancer research here on grounds of space limitation alone. A few high lights are presented with the hope of stimulating the reader to a further search of the literature and thus rousing thoughtful consideration and sympathetic encouragement of the scientists who are engaged in work on this difficult biologic problem.

## HISTORICAL REVIEW

Oncology is not a science in its own right but an application of many sciences. As such, it must draw its sustenance from the biologic and physical sciences and utilize their advances toward its particular problems. Clinical observations, classifications, and theories of cancer extend to the dawn of medical history. But it was not until the flowering of biology and pathology in the nineteenth century that a scientific approach to neoplastic diseases became feasible.

The foundation of oncology rests upon the compound microscope and the use of this instrument in the study of normal and diseased tissues facilitated by the techniques of preparation and staining of tissues for histologic examination. It was shown that the neoplastic diseases are characterized by an abnormal proliferation of cells that continue to multiply to infiltrate and to destroy contiguous tissues and to be transplanted to distant sites and grow there as metastases. In general these neoplastic cells resemble those of the tissues in which they arise or some developmental stage of the cells of the tissue in observation which adds evidence to the doctrine of cell specificity. Groups of neoplastic cells, at least by the time that they begin to break through normal boundaries of the tissue are nearly always distinguishable from other pathologic processes. It was also found that certain changes in tissues usually

hyperplastic in nature, are so often correlated with the later development of frankly malignant neoplasia that they can be designated as precancerous. It was noted that the organization of neoplastic cells often resembles the appearance of embryonal tissues, and implications of causal relationship were naturally drawn.

Johannes Muller, Leydig, Virchow, Cohnheim, and Ribbert were among the many illustrious students of the nineteenth century who laid the essential morphologic foundation of our present knowledge of neoplastic diseases. Their labors led to the description and classification of many of the tumors, to the differential diagnosis of neoplastic and other diseases, based on the procedure of biopsy, and to the description of the course, the evolutionary stages, and the culmination of the neoplastic processes. So exhaustive were the observations that few new or fundamental additions have been made to the gross and microscopic studies of morphology of neoplastic diseases since their time. The limiting factor was the power of the microscope. However, another great period of morphology is now being entered, with the application of the electron microscope.

Progress in science depends, to a great extent, upon the compilation of data derived from observations of the effects of various controllable and reproducible environments upon a relatively stable material. In the biologic sciences, this material is often some animal in which the condition to be studied can be reproduced. Experimental work on neoplastic diseases could not be undertaken on a significant scale, therefore, until material became available upon which investigations could be carried out. In 1889 Hanau successfully transplanted a carcinoma from rat to rat, and a few years later Moirau performed a similar experiment with mice. It was not until 1903, however, when Jensen's work became widely known, that the true value of their contributions was realized. A favorable experimental material had been found, and cancer research began in earnest.

The early investigators working with neoplasms arising in animals, for the most part, the mouse, had to establish that the original and the transplanted tumors were neoplastic in nature. This fact was not proved without numerous and some apparently well-founded objections from critics. Demonstrations of the development of metastases, recurrent growth, and infiltration and the careful histologic observations by Boirel in France, Michaelis and Apolant in Germany, and the workers of the Imperial Cancer Research Fund in England left no doubt that these tumors were closely similar to malignant new growths in man. The validity of using tumors in animals in cancer research is now almost universally taken for granted. This does not imply that the processes involved in the genesis of such tumors are identical, and indeed it is most dangerous to extrapolate not only from one species to another but even from one type of neoplastic reaction to other tumors.

Among the many contributions made to cancer research, the work of about ten investigators and their collaborators has been particularly outstanding. Some of these studies have extended for over twenty years, and many of the workers are still alive and still engaged in active experimentation. This

fact points out the relatively recent nature of the work and the long periods of effort and support needed for this kind of investigation

The following scientists have been singled out not only because of the importance of their original work, but also because their discoveries have opened fruitful fields for further experimentation. Rous, in 1911, elucidated the transmission of the filterable chicken sarcoma that now bears his name thus discovering the first unquestionable virus induced neoplasm. This line of investigation was extended to the mammal by Shope's discovery of the papilloma virus in the rabbit. Yamagiwa and Ichikawa, in 1918, first produced tumors in animals by long continued applications of tar, a simple method of inducing cancer in the laboratory animal, which facilitated intensive investigation of factors involved in the process. In the search for the active ingredient in tar, E. L. Kennaway and his associates in London discovered, in 1930, the first of a large series of isolated or synthetic chemical compounds, mostly polycyclic hydrocarbons, that are highly carcinogenic. C. C. Little, as early as 1909, foresaw the need of homozygous animals for the analysis of genetic factors involved in carcinogenesis, and his efforts and those of other geneticists have made available inbred strains of mice and other animals. Little and his co-workers at Bar Harbor, Maine, in 1933, established the presence of the extrachromosomal factor in the genesis of mammary tumors in mice, which led to the discovery of the milk factor by Bittner. Leo Loeb and his students were among the earliest workers on the transplantation of tumors and the influence of genetic and hormonal factors in the genesis of cancer; in 1919 they first established the role of ovarian hormones in the genesis of mammary tumors in mice. Lacassagne, in 1932, extended the work to isolated estrogenic chemicals and initiated a decade of productive investigations on this subject. Otto Warburg in his classic studies on the respiratory metabolism of cancer tissue was among the first to enlist the services of biochemistry in cancer research, a subject that has led to important observations on various enzymes and other biochemical processes and constituents of normal and neoplastic tissues.

### SPONTANEOUS TUMORS IN ANIMALS

Neoplasms of many different sites and tissues occur in all species of animals that have been studied in sufficiently large numbers for a sufficiently long period. They are found in lower forms such as amphibians and fish, and many plants develop a cellular reaction that is analogous to cancer. This wide occurrence of neoplasms in nature excludes the specific constituents of diets and other environmental exposures which man has developed in the process known as civilization from general implication as the factor responsible for cancer. The appearance of frank neoplasms in animals as in man is a relatively infrequent event in unselected populations. For practical laboratory purposes animals that are desirable for study should develop neoplasms in a fairly high incidence and should be small and easily maintained. The mouse particularly meets these requirements, and consequently most of the experimental cancer work has been carried out on this species. Investigations have

been carried out on rats, rabbits and guinea pigs, and on fowl and other birds, but on other animals the work has been more restricted and is often limited to descriptions of tumors that are incidentally encountered. The recent use of dogs in cancer research is important because so much of the work has been confined to rodents.

Practically every type of neoplasm seen in man has been encountered also in the mouse. By far the most common tumors in unselected mouse populations are the adenocarcinoma of the breast and the adenomatous pulmonary tumor. In selected groups or strains of mice, hepatomas, lymphatic leucemias, and bone tumors develop in a considerable proportion of the animals. In rats the most common neoplastic diseases are fibroadenoma of the breast and leucemia. Selected groups of rabbits have been observed to develop mammary carcinoma. In dogs mammary, testicular and adrenocortical tumors are probably the most frequent types of neoplasia. Leucemia in fowls, adenocarcinoma of the kidney in frogs, and a melanotic tumor in fish are among the so-called spontaneous tumors that have been studied in lower forms of animals. "Spontaneous tumor" is a misnomer since all that is implied is that such neoplasms appear without the intentional application of a stimulus or agent to the animal. In other words, they are tumors of unknown etiology.

### Role of Heredity

One of the first observations made on neoplasms in animals (and for the most part these were the mammary tumors of mice) was that they occurred more frequently in certain cages or groups of animals. The immediate response to these observations was the suggestion that cancer was infectious in nature. Further study showed that the neoplasms were not contagious in the ordinary sense of the term and that the distribution was determined primarily according to family relationships. Attention was then directed toward the hereditary or genetic aspects.

Slyc's publications (1914-1937) particularly stressed the recessiveness of tumor inheritance and even proposed a single-recessive factor interpretation. Later, the work of Little, Lynch and others suggested dominant inheritance of mammary and other tumors in mice. With more experience in complex characters such as tumors it became evident that no simple interpretation was possible and that susceptibility to tumors is not a character with alternative (all or none) expression but is expressed in degree. Moreover, the data indicated that all tumors could not be grouped as a single character. Lathrop and Loeb as early as 1913 were able to show that different mouse families had characteristic types of tumors, and with highly inbred strains Little convincingly demonstrated that different types of tumors are inherited as separate characters.

A major obstacle in the early work on tumor inheritance was that of heterogeneous stocks. The development of homozygous animals by inbreeding or more generations of careful brother-to-sister matings by Little, Bagg, Strong and other geneticists marks one of the great contributions that have been made toward the advancement of experimental cancer research. Inbred mice

are now considered as necessary to biologic work as are pure chemicals for chemical investigations. The use of inbred mice has permitted the observation of large numbers of genetically identical animals which develop almost every type of neoplasm that is encountered in man. Inbreeding does not influence the development of neoplasms other than in concentrating a particular type of tumor within the strain by segregation. Homozygous rats and guinea pigs also have been developed, but, in comparison with mice, relatively little work in cancer has been pursued on these species.

At present there are more than seventy strains of homozygous mice available in various laboratories in the United States. The most commonly used strains include strain A, with a high percentage of pulmonary adenomatous tumors, and, in breeding females, mammary tumors, strain C3H that develops a high incidence of mammary tumors and hepatomas, strain dba, a high mammary tumor strain, and strain C57 black, a tumor resistant strain in which mammary tumors develop in less than 1 per cent of the breeding females. Among additional interesting strains may be mentioned the strain recently developed by Strong, which has a high incidence of gastric carcinoma, Pybus and Miller's strain, which shows a high incidence of bone tumors, the I strain, with an adenomatous hyperplastic lesion of the stomach, and the high leucemia C58 and Ak strains of MacDowell and of Furth.

Analysis of the genetic factors involved in the susceptibility to these tumors, by means of hybridization experiments with homozygous mice, has been made to an appreciable extent only for mammary tumors, pulmonary tumors, and leucemia. The most significant results were obtained in experiments on mammary tumors. It was shown in investigations conducted by the Jackson Memorial group and independently by Korteweg that hybrid females resulting from the matings of high tumor strain females to low tumor strain males developed mammary tumors in approximately the same incidence as that of the high tumor strain, but when the reciprocal cross was made, that is when low tumor strain females were mated with high tumor strain males, the tumor incidence in the hybrid offspring was but little greater than that of the low tumor strain. It was obvious that an extrachromosomal factor which the female was capable of transmitting to her offspring was involved. This transmission was possible through the cytoplasm of the egg, through the placenta, or through the milk. Bittner undertook the investigation of the third possibility and by a remarkably simple procedure opened a new chapter on the problem of mammary tumors in mice. Mice of high mammary tumor strains were removed from their mothers shortly after birth and were foster nursed by low tumor strain mice. The foster nursed females developed practically no tumors and their subsequent offspring to as many as twenty tested generations remained practically free of mammary tumors. The reverse effect was noted when mice of low mammary tumor strains were foster nursed by high tumor strain females, the incidence of mammary tumors was strikingly increased. However, the incidence of tumors in later generations depends upon the genetic susceptibility of the animals. In some strains, the high mammary tumor incidence persists for many generations, in genetically resistant strains,



the incidence drops in subsequent generations. These observations have been repeated, extended, and confirmed in all details in at least six independent laboratories throughout the world.

Studies on the extrachromosomal factor in the genesis of mammary tumors in mice thus incriminated an agent or agents transmitted through the milk. Studies by Bittner and his associates and Anderson and the workers of the National Cancer Institute have added considerable information concerning the nature of this agent. Oral, subcutaneous, or intraperitoneal injection of 0.1 cc or less of milk from high-mammary-tumor strains to young animals without the milk factor leads to the development of mammary tumors some eight to twelve months later. The agent is distributed widely in the body, having been detected in the spleen, thymus, mammary tissue, mammary tumors, and the cellular elements of the blood, it apparently does not penetrate the placenta. It withstands refrigeration, desiccation, and glycerination to a limited extent and is destroyed at 60° C for thirty minutes. It is active at a pH of 5.5 to 10.2 but is inactive at pH 4.5 and is not destroyed by acetone or petroleum ether. The agent can be extracted from milk and other tissues by fractional ultracentrifugation, passes through Berkefeld filters but not through collodion membranes, and by chemical tests and ultraviolet spectrography appears to be or to be associated with a nucleoprotein complex. The properties of the agent and its obvious self-reproducibility in susceptible mice are compatible with the view that it is related to the group of disease-causing agents known as viruses. The mammary tissue requires development by hormones before the neoplastic reaction materializes, and, under usual conditions, the tumor is limited to females.

The important role of the milk factor in the genesis of mammary tumors in mice is apparently limited to mammary tumors. The milk factor is not involved in the genesis of pulmonary tumors, hepatomas, or nonepithelial tumors. There is no positive information that a milk agent or another type of extrachromosomal influence is operative in mammary carcinogenesis of other species. Reciprocal hybridization experiments are in progress in rats, and Greene states that in rabbits these factors are not evident. Interesting and important as the work may be, it is clear that extrapolation to man at this time and the obvious recommendation of complete interruption of breast feeding as a prophylactic measure against mammary cancer in man are at least premature.

Pulmonary tumors in mice are especially under the control of genetic factors. These neoplasms arise multicentrically from the lining of the alveoli, are adenomatous in appearance, grow slowly, and rarely metastasize. They can be transplanted into other mice of the same genetic constitution and upon serial transplantation rather frequently alter in morphology and become sarcomatous. Different strains of mice show extreme differences in the incidence of these tumors, practically all strain A mice develop them by the time the animals are about 18 months of age, whereas C57 black mice rarely have these tumors. The incidence and the number of tumors in the lungs can be increased by numerous agents, particularly those of the carcinogenic hydrocarbon type.

but including *o* aminoazotoluene and ethyl carbamate (urethane) The influence of the genetic factors is evident in that such procedures increase and accelerate the neoplastic reaction in the degree of susceptibility possessed by the animals, the number of tumors, the incidence, and the time of appearance in different strains are in the same order that they are when these strains develop such tumors spontaneously The extrinsic agents, therefore, merely accelerate a reaction whose essential factors are already inherent in the animal The factors may be transmitted by means other than genetic, but the occurrence of pulmonary tumors is not influenced by reciprocal crosses, thus an extra chromosomal factor is ruled out Sex and the administration of hormones have no influence on the genesis of the tumors The genetic factors influencing susceptibility are multiple and are associated with at least four known genes, flexed tail, lethal yellow, and the linked genes, shaker 2 and waved 2

Some influence which is extrachromosomal in nature is operative in the transmission of leucemia in mice Reciprocal crosses between high leucemia strains C58 or Ak and low leucemia strains showed a higher incidence of the disease among the young derived from crosses in which the maternal parent was of the high leucemia strain Foster nursing of Ak mice by low leucemia females also significantly lowered the incidence of leucemia, but this lowered incidence was not maintained in subsequent generations, and reciprocal foster nursing of low leucemia strains by high leucemia females did not increase the incidence of the disease Additional studies indicate that this extrachromosomal factor is not the same as the milk factor involved in the genesis of mammary tumors in mice

### CARCINOGENIC AGENTS

Experimentally induced neoplasms are tumors that can be evoked at will in animals exposed to certain chemical and physical substances The agents that are capable of eliciting a neoplasm are usually designated as carcinogenic By usage the term is not restricted to the induction of carcinoma but includes all neoplasms, although when only benign growths are produced, tumorigenic is preferred Direct causative relation between the agent employed and the neoplasm produced is not implied All that can be said is that following the injection or exposure to a certain procedure, certain tumors arise in significantly higher incidence than in untreated animals

Several carcinogenic agents were known from clinical experience long before the extension of the investigations to the laboratory Perhaps the first was the description by Percival Pott in 1775, of scrotal carcinoma in men exposed to constant contact with soot In 1918, Yamagiwa and Ichikawa reported that continuous painting of rabbits' ears with tar led to the appearance of carcinoma The observation was rapidly extended to the rat and mouse and the simplicity of the method led to its extensive use in cancer research The histologic and gross changes following cutaneous application, subcutaneous injection and introduction into other sites were meticulously described The influence of dosage, length of exposure various variants in

the tar, and the condition of the animals and their environment were carefully studied. It was established that not all tars were equally efficacious in eliciting neoplasms and that some were entirely devoid of activity.

### Carcinogenic Hydrocarbons

The successful search for the specific constituent active in tar was the achievement of the London group under the leadership of Kennaway and Cook. The active ingredient was found to be 3, 4-benzpyrene (Fig 3). As a matter of fact, the first carcinogenic polycyclic hydrocarbon compound to be described was 1,2,5,6-dibenzanthracene in 1930. Further modifications of the benzanthracene nucleus led to the synthesis and biologic testing of numerous related compounds by the London group, by Fieser and Shear in this country, and by others. Particular interest was aroused when one of the most active of the carcinogenic hydrocarbons, 20-methylcholanthrene, was prepared from bile acids. The structural resemblance among the carcinogenic hydrocarbons, cholesterol, bile acids, and the steroid hormones that were also being isolated and synthesized during this period developed high hopes that a common molecular structure and the physiologic elaboration by the body of compounds similar to the hydrocarbons could clarify the cancer problem.

The carcinogenic hydrocarbons can well be termed "almost universal carcinogens," at least as far as the mouse and rat are concerned. Biologic testing is usually restricted to skin painting, which evolves cutaneous carcinomas, or to subcutaneous injection, which induces sarcomas at the site of injection. The preponderance of sarcomas following injection into other sites, however, is probably due to the highly reactive connective tissue of mice and rats and to the destructive action of the carcinogen on the more complex tissues at the dose and in the form in which it is usually administered. Nevertheless, carcinoma of the kidney and the stomach, brain tumors, and rhabdomyosarcomas were elicited upon injection into appropriate tissues. The feeding of carcinogenic hydrocarbons evoked intestinal adenocarcinomas in mice, and intravenous injection increased the number of pulmonary tumors. The action was not limited to the site of application. Pulmonary tumors appeared following subcutaneous injection, and mammary tumors and leukemia were evoked in certain strains of mice. The appearance of mammary tumors was particularly interesting since the results were obtained in mice apparently lacking the milk influence.

Subcutaneous, cutaneous and brain tumors were also produced in the rat, and with somewhat larger doses, fibrosarcomas and liposarcomas appeared in guinea pigs at the site of injection. Painting of rabbits with carcinogenic hydrocarbons was not so efficacious in producing cancer as was tar, a fact which suggested the presence of other active or additive substances in tar. Other species that have been tested, not so exhaustively as the laboratory rodents, have been much more resistant to carcinogenesis. Melanomas and other skin tumors appeared in dogs following seven years of continual application of tar. At Yale, monkeys have not yet developed tumors after repeated treatment with large doses of carcinogenic hydrocarbons.

It was soon found that even in mice the carcinogenic reaction was influenced by so many factors that only a relative definition was feasible of the property of carcinogenesis of any chemical, since it was modified by the strain of animal, its age and condition, the site, method, and dose of injection, and the physical state of the preparation. In a homogeneous group of susceptible animals the response was correlated with the logarithm of the dose, 0.004 mg of two active hydrocarbons being sufficient to produce sarcomas at the site of injection.

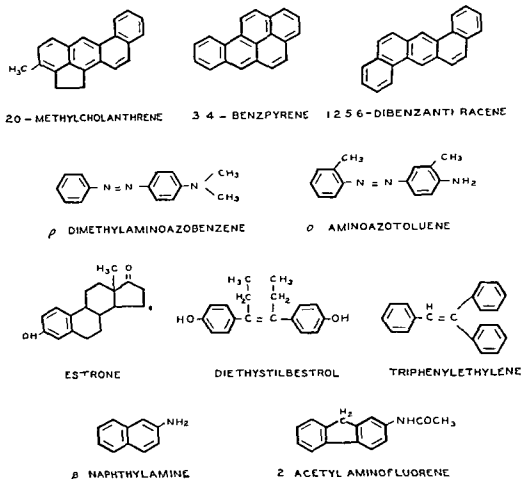


Fig 3—Some carcinogenic compounds

Appearance of subcutaneous or cutaneous tumors in mice or rats followed the application of many other chemicals that could not be related to the polycyclic hydrocarbons in molecular structure. The list includes such compounds as potassium hydrochloride, hydrochloric acid and concentrated solutions of sugar. It is true that whereas with the hydrocarbons one injection suffices, these agents have to be given repeatedly over long periods. Moreover, tumors are not produced so often and with equal dispatch as are those obtained with a single injection of the highly active carcinogenic hydrocarbons. These differences may be attributable to the relatively easy destruction and elimination of some of these substances whereas the hydrocarbons for the most part are relatively insoluble and are retained at the site of injection for long periods.

That the human body contains carcinogenic chemicals was found by Shabad, who elicited some sarcomas and an increase in the number of other tumors in mice injected with extracts of liver from patients with cancer. This work has now been confirmed by at least four investigators, although active extracts were obtained from other tissues as well as from liver and from organs of noncancerous individuals. Activity is found in the nonsaponifiable fat fractions. Identification of the active chemicals has not been achieved as yet and is awaited with great interest.

### Estrogens and Other Hormones

Among the chemical compounds whose carcinogenic action is limited to certain specific tissues are the estrogens, a generic term that includes synthetic chemicals, such as diethylstilbestrol and triphenylethylene (Fig 3), as well as physiologically produced chemicals with estrogenic activity. These compounds may be characterized as growth stimulants of genital and accessory tissues, and under normal conditions the phenomenon is cyclic or rhythmic in nature.

The association of estrogens with cancer was first ascertained from experiments on mice. Mammary cancer in mice is sex-limited to females. Oophorectomy at early ages decreases and reproductive activity increases the incidence of mammary tumors, and subcutaneous grafting of the ovary into castrated males results in the appearance of mammary tumors. With the isolation and synthesis of female sex hormones, Lacassagne was able to induce mammary tumors by injecting the chemicals into male mice. The experiment might be interpreted as indicating that estrogens directly elicit abnormal or malignant growth or that they merely induced mammary proliferation so that it allows the exteriorization of the neoplastic reaction produced by other factors inherent in the animal. Extension of the studies by Lacassagne and others showed that male mice from strains in which the females develop mammary cancer acquire such tumors after the injection of estrogens but that males belonging to strains in which such tumors are not observed among the females do not. Numerous investigations were performed to determine the nature of this susceptibility and resistance of different strains, but differences in the estrus cycle, the amount of estrogen needed for the vaginal response, the quantity of hormone excreted in the urine and the morphology of various endocrine organs could not be correlated with susceptibility to mammary carcinogenesis. The susceptible mice did not have consistent abnormalities of the intrinsic hormonal environment but did show localized areas of hyperplastic epithelial tissue in the breast, which are rarely found in the low-tumor strains. Much of the clarification of the problem resulted from the discovery of the milk factor in mice. It was shown that the induction of mammary tumors in male mice depended upon whether such mice had the milk agent. Thus estrogens cause the exteriorization of the action of the milk agent on the mammary tissues by bringing it to the proper functional and anatomic level of development. On the other hand the milk agent is ineffective in producing mammary tumors without the creation of a suitable substrate by the estrogenic and other hormones.

The amounts of estrogenic hormones necessary for mammary carcinogenic action depend upon the physiologic potency of the compounds. Within limits, the larger the amount of estrogen administered, the earlier mammary tumors appear, and in higher incidence. Treatment must be prolonged for at least eight to twelve weeks if preparations of relatively short duration such as oily or aqueous solutions are employed. A single subcutaneous implantation of crystals or pellets producing constant, prolonged absorption of the chemicals is sufficient to elicit mammary tumors at doses calculated to be not above those physiologically produced by mice.

Mammary cancer has been induced in a high proportion of male and female rats of some colonies treated with large doses of estrogen. Mammary cancer is relatively rare in female rats under normal conditions. Morphologically benign fibroadenomas of the breast occur more frequently, particularly in the Albany strain of rats, which show a high incidence of sterility, irregularity of estrus cycles, and hypophyseal adenomas. Mammary cancer in the rabbits studied by Greene was associated with pre-existent inflammatory cystic disease of the breast, and the animals exhibited manifestations of hyperestrinism. The induction of mammary cancer in rabbits treated with large doses of estrogen has been reported by one investigator. Prolonged periods of treatment of monkeys with large doses of estrogen have not led to the appearance of mammary cancer.

The injection of estrogens into experimental animals for prolonged periods has led to the appearance of several other types of tumors. Fibromyomatous overgrowths are produced in the subserosa or myometrium of guinea pigs. These growths appear throughout the abdominal cavity, and, although they invade contiguous organs, the tumors regress when estrogenic treatment is discontinued. In mice, malignant epithelial growths of the uterine cervix were elicited in over 50 per cent of the animals that received 166 of estradiol benzoate weekly for one year or more. In strains A, C and JK, prolonged treatment of males leads to the appearance of tumors of the interstitial cells of the testis.

Prolonged treatment with large doses of estrogens leads to hypertrophy of the prostatic gland in dogs. The pituitary of rats and of certain strains of mice also hypertrophies. The pituitary tumors in mice and rats are chromophobic adenomas, and the larger tumors in mice can be transplantable into other mice of the same strain.

The incidence of lymphatic leucemia and of estrogenic tumors is increased among mice of some strains subjected to estrogenic treatment.

Estrogenic compounds, therefore, initiate in some unknown way a number of neoplastic processes usually of tissues that are normally under the influence of sex hormones. As Gardner states there is evidence that estrogens merely facilitate the materialization of certain potentialities which are transmitted to the organism. Other steroid hormones do not possess the property of directly or indirectly leading to the development of neoplasia. Progesterone and testosterone inhibit the carcinogenic potency of the estrogens, prolonged treatment with these compounds reduces the incidence of mammary tumors in mice and

the fibromuscular reaction to estrogens in guinea pigs. Desoxycorticosterone does not influence the development of mammary tumors. Grafts of the pituitary gland stimulate the appearance of mammary tumors, but only in the presence of the ovary. An interesting exception may be the hormones of the suprarenal cortex. Castration of mice of certain strains leads to the appearance of hyperplastic nodules in the suprarenal cortex which in strain ce culminate in frank cortical carcinomas. The suprarenal glands compensate for the removed gonads, since the original castrate state is overcome and mammary tumors appear.

### Azo Dyes and Other Compounds

The frequent occurrence of cancer of the bladder in workers in the aniline dye industry led to the study of various chemicals in this group. Prolonged exposure of rabbits to the vapors of *N*-naphthylamine or the subcutaneous injection of the compound into dogs led to the appearance of papillomas and carcinomas of the bladder.

A similar site specificity has been determined for a group of azo dyes. When incorporated into the diet and fed to rats, *o*-aminoazotoluene and *p*-dimethylaminoazobenzene (Fig. 3) produce *emihotic* changes and eventually carcinoma of the liver. The latter compound is more active for the rat than the mouse, whereas *o*-aminoazotoluene is more effective in the mouse than in the rat. The specificity for the liver is only relative, however, since the incidence of pulmonary tumors is increased, and hemangioendotheliomas in subcutaneous and intraperitoneal sites are induced in some strains of mice. One investigator has reported the appearance of sarcoma at the site of subcutaneous injection.

Work with the azo dyes incriminated diets as an important contributory factor in the development of tumors of the liver. In general, tumors appear earlier and in a higher incidence in animals on deficient diets, and the neoplastic reaction is delayed with diets containing high protein and high vitamin B complex levels. This effect may be attributable to the detoxification and elimination of the azo compounds as well as to the direct protection of the liver cells against carcinogenic action.

Hepatomas in mice can be induced also by protracted feeding of carbon tetrachloride or chloroform and in rats, with diets containing selenium. These chemicals first elicit conspicuous *emihosis* in the liver, and the neoplasms arise subsequent to the *emihotic* changes. It has recently been found, by carrying out the dose-response curves to the lower extremes, that *emihosis* is not an essential precursor to the neoplastic reaction. No tumors other than those of the liver have so far been described following ingestion of carbon tetrachloride or chloroform. An insecticide, 2-acetyl-aminofluorene (Fig. 3), on the other hand induces not only hepatomas in rats, but also carcinoma of the breast, sweat glands, and kidney.

The number of carcinogenic chemicals is apparently limited only by the patience of chemists to synthesize or to isolate them and by the patience of the biologists to test them on a sufficient number of animals of various species by various routes of administration. In 1941 Hartwell collected data on 696

chemicals that had been tested, and of these 169 were reported to be carcinogenic, since then, more than 100 other compounds have been added to the list. The search for a correlation between molecular architecture and the property of carcinogenesis seems futile except within the narrow confines of definite chemical groups. Nor does there seem to be any common physiologic action that can be attributed to all the chemicals that are able to provoke the neoplastic reaction. Furthermore three important classes of carcinogenic agents still remain to be mentioned: physical agents, parasites and viruses.

### Roentgen Rays and Ultraviolet Radiation

The fact that roentgen rays and radium are carcinogenic was first shown by the tragic development of skin carcinomas in physicians and other workers within ten years after the discovery of roentgen rays. Clunet reproduced the process in rats by repeatedly exposing them to roentgen rays. This method of inducing cancer in experimental animals has not been widely applied, although neoplasms have been elicited in rats, rabbits, mice, and guinea pigs. The most popular technique has been the introduction of radium needles or capsules or impregnated strings into various sites. Osteogenic sarcomas followed its insertion into rabbit femurs and carcinoma of the gall bladder followed its introduction into that organ. Thorotrast also has produced sarcomas after its subcutaneous injection into rats and mice. Total irradiation of the mouse with roentgen rays leads to the development of granulosa cell tumors of the ovary and an increase or an earlier appearance of leucemia.

The induction of tumors following exposure to ultraviolet radiation was first recorded in the rat by Findlay and similar exposure of white rats to sunlight also leads to the appearance of skin carcinomas. The effective wave length was found to be below 3200 Å. The production of tumors depends upon the quantity of radiant energy applied rather than upon its intensity and a quantitative relationship has been established between the dose of radiation and the neoplastic reaction. In white mice a great number of sarcomas as well as carcinomas appear, probably because the thin skin of the mouse allows increased penetration of the radiation.

The action of these two forms of energy in producing neoplasms is no more clearly understood than is the induction of tumors by other agents. Roentgen rays are known to produce mutations in sex cells and it has been assumed that a similar change occurs in somatic cells. It is difficult to understand why the latent period between exposure to roentgen rays and the appearance of cancer is so prolonged if a direct mutagenic action is exerted on the cell. It would be necessary to attribute to the carcinogenic hydrocarbons and certain viruses even greater potency to induce mutation, an entirely unestablished point, in order to support this as a common characteristic of carcinogenic agents and processes. That a different type of action may be involved in the induction of neoplasia by ultraviolet radiation and carcinogenic hydrocarbons is indicated by showing that the action of these two agents is not additive.



## Parasites

The increased incidence of cancer of the urinary bladder following infestation with bilharzia and the correlation between the presence of liver flukes and carcinoma of the liver were known from clinical experience by 1900. Fibiger's classic study on the relation of gastric carcinoma in rats with infestation of a parasitic worm, whose larval stage is in the cockroach, was probably complicated by a concomitant dietary deficiency in vitamin A. Several other parasitic infestations induce neoplasms, perhaps the most consistent one being the appearance of sarcomas of the liver in rats following ingestion of *Taenia crassicolis*, which in the rat encysts itself in the liver.

The action of these larger parasites in producing neoplasia must be an indirect one. The usual explanations offered include most cancer theories: they may act as chronic irritants, produce or cause the production of carcinogenic chemicals, carry a virus, or initiate a somatic mutation.

The production of neoplasia in animals by bacteria, yeasts, or fungi has been rather conclusively disproved. In a variety of plants, overgrowths of abnormal cells which invade and destroy contiguous tissues and which disseminate to other portions of the organism and grow as metastases can be induced with *Phytophthora tumefaciens*, a bacterium first described by Erwin F. Smith. Metastases may be free of the organism, and the tumors may be thus transplanted without further intermediation of the bacterium. Whether crown gall of plants is similar to cancer of animals is unknown, but this interesting cellular reaction in plants has not attracted the attention it deserves from scientists concerned with cellular physiology of neoplastic diseases.

## Viruses

The unsuccessful investigations that attempted to prove bacterial etiology of cancer and the experiments on transplantation of tumors which indicated that such transfer is effected only by means of living cells led to early conclusions that cancer was not an infectious disease. This period coincides with some of the earlier work that established submicroscopic entities, known as viruses, as pathogenic agents.

Rous, working between 1910 and 1914 at the Rockefeller Institute on forty spontaneous tumors of chickens, five of which were transplantable, showed that these tumors could be transferred by cell-free filtrates. One of these neoplasms was the source of the Rous sarcoma. At the same time, Fujinami and Inamoto also reported a filterable myxosarcoma in the fowl, and other investigators added several other types of malignant connective tissue neoplasms. Subsequent work established beyond doubt that these were neoplasms and that the presence of living tissue cells in the filtrates could be excluded. Passage through graded filters determined the size of the particles with which activity was associated at 100, and the activity was destroyed not by drying or glycerolation but by heating for thirty minutes to 60° C, by formaldehyde, bichloride of mercury, or by iodine.

Injection of the active filtrates results in the appearance of sarcomas at the site of injection or at sites of injury, such as the needle tract or a distant area that is wounded. The tumors appear much quicker than with any other carcinogenic agent, in a matter of days, whereas the most active carcinogenic hydrocarbons require about four weeks for the appearance of the first tumors. The inciting agent is often recoverable from the tumors, and since its activity is not diluted out on serial passage, it must be self reproducing or must cause the production by the body of additional quantities of the agent. Recent work by Claude and others, in which highly purified fractions were obtained by ultracentrifugal separation, indicates that activity is associated with a complex nucleoprotein of which pictures can be obtained with the ultramicroscope. Whether these particles are the viruses or whether the active component is merely associated with the particles is not established since similar bodies can be separated from normal cells.

The chicken produces antibodies to the Rous agent but neither active immunity nor passive immunity conferred by injection of immune serums from other species protects against the transplantation or growth of established sarcomas, presumably because the active agent is protected by its intracellular position. The Rous agent, as are the tumors induced by it, is species specific under usual conditions. Interesting experiments of Duran Reynals showed that it can be transmitted successfully to other birds, such as ducks, turkeys and guinea fowls, by intravenous injection into newly hatched animals. The tumors that appear within a month after the introduction of the agent can be returned to the chicken, but in later tumors the agent subsequently maintains its developed adaptation for the duck. Also, hemorrhagic lesions rather than tumors may appear and the tumors may localize in sites and tissues different from those in the chicken, such as in bones.

Among the virus induced tumors may be included an erythroblastic leukemia of chickens but objections that such tumors are limited to birds are discounted by the extension of similar findings to the rabbit. Shope, in 1933, discovered that a papilloma occurring in wild rabbits could be transferred by glycerolated tissue or filtered tissue extract into domestic rabbits and that many of these lesions became frank carcinomas in the domestic rabbit, but its presence is signified by the appearance of antibodies in the blood as the tumor develops.

There is evidence that the adenocarcinoma of the kidney in frogs is associated with a viruslike agent. It has already been indicated that the milk agent necessary for the appearance of most of the mammary tumors in mice also fulfills the characteristics for being classified in the same category.

There is no question therefore, that at least three types of neoplasms in mammals as well as in birds are induced by self perpetuating submicroscopic entities whose activity is associated with a nucleoprotein complex. On the other hand whether all neoplasms are due to viruses and whether the viruses are not merely initiators of the neoplastic reaction but are more intimately

involved in the cancerization process of the cell are interesting speculations. It is fortunate that the rapid strides being made in the studies of other virus infections will permit experimental approaches to this intriguing problem.

### PRECANCEROUS CHANGES

Discovery of carcinogenic agents allowed systematic investigations of morphologic changes that occur in tissues between the introduction of the agents and the appearance of neoplasia. Careful microscopic studies have been made on pulmonary, subcutaneous, cutaneous and hepatic tumors in mice and on mammary tumors in mice and rats and on virus-induced tumors of chickens and rabbits. Tumors induced with tars were always associated with inflammatory changes due to the many mutants in the material. With carcinogenic hydrocarbons the presence of an inflammatory reaction is not an essential precursor of neoplasia.

Within two weeks following subcutaneous injection of carcinogenic hydrocarbons into high-pulmonary-tumor strains of mice there is a diffuse cellular increase involving the alveolar wall, with large pale cells resembling alveolar phagocytes partly projecting into the lumen. Focal accumulations of these cells are observed during the fourth week and by the fifth week the pathologist recognizes them as small tumors. Histologic appearance of larger tumors is usually that of an adenoma, but gradually the tumors invade and destroy the contiguous tissue and are transplantable and some metastasize to the regional lymph nodes.

Histologic and cytologic studies of premalignant changes in the subcutaneous tissue around a carcinogenic hydrocarbon show the presence of atypical connective tissue cells but correlation between the histologic characteristics of the tissue and its transplantability is not certain. It is suggested that malignant changes may have been induced before the necessary criteria for the histologic recognition of malignancy became fully established.

Mammary tumors in mice and rats originate multicentrically from the cells of the mammary epithelium. During the transition from the normal to the neoplastic tissue there is no evidence of a sudden morphologic alteration but an indication of a gradual change from the resting epithelium through hyperplasia with gradual appearance of alterations that turn imperceptibly into frank carcinoma. Inflammatory reaction is not a necessary concomitant in the process. In rabbits most mammary tumors arise on the basis of recurrent cystic mastitis but some of the tumors originate from adenomatous nodules occurring in otherwise normal breasts.

The earliest changes in tissue following injection of Rous virus so far always mixed with other tissue material are a collection of monocytes and a proliferation of endothelial cells. Surrounding this primary lesion there is a gradual hyperplasia of fibroblasts of atypical morphology. The increase in this fibroblastic reaction and invasion of contiguous tissues is designated as the appearance of the tumor. With the Shope papilloma virus, there is a gradually increasing amount of hyperplasia of epithelial cells. If the outward

piling up of the epithelium is prevented by collodion or if the cells are transplanted to subcutaneous sites, the benign tumor extends beyond its boundaries and assumes characteristics of malignancy.

From these and other studies it may be concluded that inflammatory reaction is not a necessary precursor of the neoplastic reaction. It is also clear that there is no definite morphologic point at which normal cells under the stimulus of a carcinogen become abnormal, or between the accumulation of new cells, whose appearance is benign, and the development of frankly invasive neoplasms. In a few instances, such as the characteristic alteration in the mitochondria and the Golgi apparatus of hepatomas in mice, single cells may be sufficiently different from surrounding normal cells as to be recognized as neoplastic. In general, however, it has not been possible to establish the existence of a strictly specific characteristic of a cancer cell. Nor is there a clear boundary between tumors that are designated as benign and malignant. The most reliable criterion is the penetration of such cells beyond normal boundaries which is merely a stage in a continuous process. Greene has recently suggested that even this local invasiveness is not too certain a criterion of malignancy and that an even greater degree of autonomy developed or acquired gradually by tumors and manifested by the appearance of metastases is more truly indicative of a malignant neoplasm.

### CARCINOGENESIS IN VITRO

The neoplastic reaction has been observed in tissue cultures as well as in animals. These experiments are important because they indicate that the neoplastic process is probably a local one in that it does not require systemic alterations involving the whole organism and they furnish additional evidence of the cellular nature of the neoplastic reaction.

Malignant change has been reported in chicken fibroblasts grown in tissue culture to which dibenzanthracene was added. The results were probably due to the presence of the Fujinami virus in the tissue, and it is uncertain whether the cells were altered *in vitro* or whether the agent was merely transferred to the chickens into which the cultures were implanted.

Recently, two investigators have reported the neoplastic transformation of mouse fibroblasts grown in tissue culture. In one experiment, the alteration was tentatively attributed to exposure to roentgen radiation. In an exhaustive study, Earle noted that following the addition of methylcholanthrene to the nutrient fluid the most significant alteration in the tissue clumps was the tendency of cells to adhere to each other, forming epithelial like sheets. This alteration in cell surface was apparently permanent for it remained unchanged long after the withdrawal of methylcholanthrene and after transfer of the tissue into new nutrient media for as many as a hundred times. In a second series, the altered tissue clumps produced sarcomas at the site of implantation into mice, and the tumors were carried on by successive transplantation. The role of the carcinogen is obscure since with an increasing period of exposure the main effect was to depress the growth of the culture and to produce greater morpho-

logic alterations, while actually fewer sarcomas were produced on injection into animals than occurred with cultures which had contact with the carcinogen for only six days. In fact, the highest percentage of tumors was obtained from control cultures that had been grown on heterologous media and had had no known contact with methyleholanthrene, although trace contamination could not be ruled out. On the other hand, tumors that arose from cultures exposed to methyleholanthrene for over one hundred days showed more mitoses, metastases, and local invasiveness.

In these experiments, one type of mammalian cell was converted into neoplastic cells *in vitro*, entirely removed from the systemic reactions of the original host and in an entirely heterologous culture medium. It is significant that there were no sudden morphologic or biologic alterations during the course of the experiments but that the morphologic changes were cumulative.

## CHARACTERISTICS OF ESTABLISHED NEOPLASMS

### Chemical Characterization of Neoplasms

In comparison with the advances made in the understanding of some of the etiologic factors involved in the genesis of certain types of neoplasms, knowledge concerning the growth of established tumors from physiologic and biochemical aspects has remained scant. At least the manifold isolated observations on various tumors do not fit into a pattern whose significance can be readily appreciated, particularly difficult is the estimation of whether such findings are related causally or intrinsically to neoplasia or are secondary, nonspecific effects.

Chemical analyses of various inorganic and organic constituents of tumors reveal no findings that can be considered as characteristic for neoplasms, either qualitatively or quantitatively. Extension of biochemical work to metabolism, however, has revealed some interesting facts. The most valuable contribution in this field has been that of Warburg, which led to the discovery of rather characteristic metabolic properties of neoplastic tissues. It was found that the suppression of glycolysis in the presence of oxygen fails to occur or is considerably reduced in neoplastic tissue. Tissue slices of malignant tumors treated with glucose under aerobic conditions accumulate more lactic acid than do most normal tissues and benign tumors. This fact can be confirmed by *in vitro* studies. Injection of glucose into the tumor-bearing animals produces a drop in the pH shown by the tumors. By consideration of the absolute and relative magnitudes of anaerobic glycolysis, of the respiratory quotient, respiration, and aerobic glycolysis, and quotients derived from these figures, about 95 per cent of all tumors fall within certain definite categories. The small reserve of cytochrome *c* and of zymohexose in tumors would indicate that metabolic functions of tumors are conducted at a minimum level.

Greenstein has studied a number of enzyme systems in a wide variety of tumors. In comparison with normal tissues of origin, the activity of various enzymes may decrease, increase, or show no alteration. Thus, each tumor type has its own characteristic mosaic of enzymes. However, the range of enzy-

matic activity is much smaller among tumors than among normal tissues, probably because of the decrease of specific function in the tumor

The concentration of vitamins is also more uniform among different tumors than in normal tissues from which the tumors are derived. Particularly in the case of biotin, the vitamin content of a tumor deviates from its homologous normal tissue in the same direction as corresponding embryonic tissue.

The range of concentrations of enzymes and vitamins among all neoplasms is much narrower than among normal tissues. Neoplasms converge toward a group of tissues of rather uniform biochemical type, as is also indicated by studies on respiration and glycolysis. In a few properties, there is an overlapping of some normal tissues and tumors and benign growths in general fall between these categories. These conclusions are almost identical with those reached in the studies on histology. Up to the present, it has not been possible to utilize the biochemical characterizations of neoplasms either in clarifying their genesis or in chemotherapy.

### Properties of Tumor Susceptible and Tumor Bearing Animals

The chemical constitution of the tissues of each species and strain of animals may be considered unique for that species or strain. Some attempts have been made to correlate certain chemical findings in tissues with susceptibility to neoplasia, for example the amount of porphyrins or the level of the serum esterase. Such attempts have not been successful, probably because different tumors require different conditions for their genesis. In mammary tumors in mice, at least three factors, genetic, hormonal, and the milk agent, are involved. Biochemical and other differences may be related to genetic susceptibility, to the hormonal status or to the presence or absence of the milk factor. Without distinguishing at least these three factors, it is impossible to evaluate over all differences. For the genesis of specific tumors, certain biochemical alterations are definitely required. For example the castrate state and its hormonal imbalance are required for the genesis of adrenocortical carcinoma in strain ce mice. Alterations in the biochemical status of the host may influence the growth of certain tumors. Interstitial cell tumors of the testes in mice seldom grow unless the host is estrogenized and the growth and morphology of the adenofibroma of the rat is greatly influenced by estrogens and androgens.

The presence of a tumor may evoke systemic reactions in the host in a site far removed from the neoplasm. Cachexia, anemia and the hepatic dysfunction in patients with gastrointestinal cancer are examples frequently encountered in the clinic. In animals the catalase activity is lowered in the liver and kidneys, the red cells and hemoglobin decrease, the blood protease increases, the plasma xymohexose increases and the serum and tissue esterase decrease. There is also a loss of fatty material from the suprarenal cortex. These changes occur with a variety of tumors and many of the alterations return to normal levels following regression or removal of the tumor. The effects are detectable when the tumor weight is an appreciable fraction of the body weight of the host, thus invalidating the application of the findings to clinical diagnostic use. It is not definitely known whether these effects are unique for

neoplasms, but they are not due merely to the presence of growing tissue. It is also significant that some enzyme systems are not affected by tumors. The mechanism of the changes is obscure, although the low hemoglobin and catalase in tumor-bearing animals suggest some interference with hematin synthesis. The decrease in the lipoids of the suprarenal cortex and the appearance of highly oxygenated ketosteroids in the urine of patients with advanced cancer suggest abnormalities in the metabolism of cortical suprarenal hormones.

In contrast with the systemic effects of neoplasms in general should be mentioned the effects of certain specific neoplasms. The increase in the serum acid phosphatase activity in disseminated prostatic carcinoma and of serum alkaline phosphatase in osteogenic sarcoma, the appearance of melanin in the urine of patients with melanoma, the hyperinsulinism due to tumors of the islands of Langerhans, and the manifestations of hormonal abnormalities, both clinically and by various chemical tests on the urine and blood, in patients with carcinoma of the suprarenal cortex, ovarian testicular, pituitary, and other endocrine tumors have been applied as diagnostic procedures of considerable value. These effects are not due to neoplasia *per se* but to the maintenance of function or hyperfunction by neoplastic tissue derived from such organs.

### Transplantation of Tumors

One of the more fundamental characteristics of established neoplastic tissue is its ability to grow progressively in sites other than that of origin. This characteristic of increased autonomy is manifested in the occurrence of metastases. Historically, the finding that neoplasms can be transferred to other hosts of the same genetic constitution, thus allowing extensive studies on this material preceded investigations on carcinogenesis.

Transplantable tumors are neoplasms that have arisen spontaneously or following some induction procedure and have been transferred by successive passages to other animals. Living cells must be inoculated, and these cells must adapt themselves to the new environment. All transplantable tumors are a form of tissue culture, descendants of the cells of the original tumor, and are not produced by the new hosts except inasmuch as to furnish the necessary nutrition and other conditions necessary for further growth.

The adaptation of transplanted tumor cells to the new host is usually dependent upon the use of a host of the same genetic background as the animal in which the original tumor arose. Otherwise the transplanted tumor cells are destroyed, probably because of the immunologic defenses of the host against the foreign proteins of the tumor. According to Little, genetics of tissue transplantation has a Mendelian basis, and the number of genes involved varies in individual cases according to the degree of genetic similarity or difference between donor and host. Occasional heterologous transplantations of tumors are recorded in the literature, but usually special conditions are necessary for successful transplantation to other species. Heterologous transplants to the brain and to the anterior chamber of the eye have been successful, the defense reactions in those sites are apparently less effective than in the subcutaneous and other tissues.

Viable tumors may also be maintained on chick embryo, as shown by Murphy in 1913 and recently modified by the use of the yolk sac method, and on tissue culture media by methods devised by Harrison and Carrel

It should be pointed out that the ability to survive upon transplantation is a property not limited to malignant tumors. Normal tissues, embryonic tissues, and benign tumors can also be maintained in tissue culture, and, if homozygous animals are used, in the tissues of a new host. Under most conditions, however, such transplants do not grow progressively. Survival and growth upon transplantation is, in a measure, a manifestation of the autonomy of the neoplastic tissue. This characteristic is evident in healthy hosts inoculated with tumor tissue as well as in animals in which the tumors originate and is probably a manifestation of acquired properties of tumor cells rather than of a breakdown of the mechanism of resistance of the host, although obviously the end product is the result of the interaction of the two factors. There seems to be increasing evidence that cancer cells infiltrate and destroy not only because of an exuberance of normal reproductive processes but also because the tissues of the host are subjected to the action of some specific products of neoplastic cells. Observations on growing transplanted tumors by means of the transparent chamber technique indicate that the tumors continually stimulate the production of new vascular channels in order to sustain growth. Recent work by Ludford also indicates that carcinoma grown next to normal fibroblasts in tissue culture accelerates the growth of such fibroblasts, whereas sarcoma inhibits them. Identification and quantitative measurement of the chemical substances that must be produced by cancer cells in order to stimulate the proliferation of blood vessels and of fibroblasts may well be an essential clue to the mechanism by which cancer infiltrates and destroys.

A finding that has attracted attention of cancer investigators is the occasional transformation of transplanted carcinoma into sarcoma. It has never been established whether such transformation is due to selective survival of sarcomatous elements not noted in the original possibly mixed tumor, or whether the cells of the carcinoma in some way react on the stroma. In fact, some pathologists notably Ewing have maintained the view that such sarcomatous transformation is merely an alteration in the shape and other morphologic characteristics of epithelial cells.

### Prophylaxis and Therapy

Prevention of neoplasms depends upon the knowledge of etiologic factors and the removal or neutralization of such factors. In this manner, the protection of mice against exposure to the milk agent prevents the occurrence of most mammary tumors in this species. Immune serum obtained from rabbits receiving the milk factor protects mice into which the milk agent is subsequently injected.

More general protective measures against neoplasms based on attempts to increase the resistance or to decrease the susceptibility of tissues to the neoplastic reaction, have been of very limited success. Perhaps the most inter-



esting results have been obtained in investigations on diet. Reduction of the total diet by underfeeding or of specific constituents thereof reduces markedly the incidence of mammary tumors in mice. It is very probable that the effect is due to alteration in estrogenic and other hormonal secretions. Underfeeding also reduces the incidence of leucemia and of chemically induced subcutaneous and cutaneous tumors. Deprivation of sulfur-containing amino acids in the diet of mice produces a radical decrease in leucemia following cutaneous applications of methylcholanthrene. The studies indicate that the carcinogens are ineffective unless acting on growing tissue or tissue possessing the necessary nutritional and other factors essential for growth. On the other hand the development of hepatic tumors in rats following ingestion of *p*-dimethylaminoazobenzene is prevented or delayed by diets adequate in proteins and vitamins and is accelerated by diets poor in proteins and vitamins. Broad generalizations on the effect of nutrition on carcinogenesis are not justified from these interesting results.

Numerous workers have attempted to influence the growth of transplanted and of spontaneous tumors in animals. Literally thousands of chemical substances and crude extracts have been tried empirically for their possible therapeutic effects but unfortunately none of the efforts has been rewarded by the discovery of a cancer cure.

As in carcinogenesis, the growth of tumors is dependent upon the nutritional status of the host and so far no specific dietary deficiency has been found which selectively restricts the growth of tumors without affecting the host as well. Restriction of essential protein constituents and of vitamins usually produces effects on tumors only at levels that seriously interfere with the host's existence.

Immunity to tumor growth was a field for avid experimentation during the early part of the century. Animals in which transplanted tumors regress are usually immune to further inoculations of the same tumor. Such immunity, either natural or induced, can be reduced or entirely broken down by several methods including reticuloendothelial blockade by means of injection of trypan blue or by exposure to roentgen rays. Unfortunately induced immunity or passive immunity applies only to transplanted tumors. Such immunity does not protect the host from developing or growing neoplasms of spontaneous origin or tumors following the administration of carcinogenic chemicals. This difference between transplanted tumors and tumors actually derived from the tissues of the animal has been the foundation of numerous premature descriptions of successful experimental therapeutic procedures. Transplanted tumors have been 'cured' by numerous agents, but the extension of the work to spontaneous tumors in each instance has led to disappointing results. The material is still useful for this type of investigation but any results based solely on it must be considered as unproved until extended to naturally occurring tumors.

It must be admitted that experiments on immunity to tumors have been extremely crude. Usually the whole tumor including the stroma, or some simple extracts have been used as the antigen. The result is that immunity

to a complex of foreign proteins and other substances has been produced. It is quite possible that much greater separation of cancer cells, either by chemical or by physical methods, may isolate a substance that may be more specific against cancer, or at least against certain types of cancer.

## CANCER THEORIES AND CONCLUSIONS

The complexity and seriousness of the cancer problem have led to so much theorizing and speculation that Rous justifiably labeled cancer as one of the last outposts of metaphysics in medical science. Most of the theories that have been offered regarding the cause or the nature of cancer fall into one of the following categories: (1) embryonic, (2) biochemical, (3) infectious agents or (4) genetic.

The morphologic resemblance between certain neoplasms and embryonic tissues naturally suggested a possible causal relationship between these two types of tissue. Cohnheim postulated that neoplasms arise from embryonal cells which have persisted and which retain a special proliferative potency. Ribbert's modification of the theory was that differentiated but embryologically displaced cells serve as foci for the genesis of neoplasia. These embryonal theories were extremely helpful in explaining the occurrence of such tumors as teratomas and the origin of tumors in tissues that normally do not possess the type of cell which these tumors exhibit. There is insufficient evidence that embryonic cells or tissues are more liable to carcinomatous transformation than are more differentiated cells. Moreover, there is little basis other than morphologic resemblance, for considering that cancer is a manifestation of incomplete or aberrant differentiation from embryonic elements. Even if it is assumed that all tumors arise from embryonic remnants, the theories cast no light upon the nature of the transformation of such cells into neoplasms.

An important variant of the concept that the presence of special cells is required to explain cancer postulates that normal cells are sensitized by certain agents or processes thus acquiring special properties that make them more liable to carcinogenesis. Perhaps the most popular of these theories is that cells become allergic and recently the porphyrins have been suggested in this capacity. The role of sensitizers is based primarily on imagination although a complex array of analogy to other conditions can be marshaled.

The biochemical theories assume that certain specific biochemical or biophysical alterations in the environment of the cells cause the cells to acquire neoplastic properties. Virchow's theory of chronic irritation may be considered under this heading, the inflammatory reaction being a morphologic evidence of altered biochemical or biophysical conditions. It is clear that inflammation per se does not lead to neoplasia and that several types of experimental neoplasia can be elicited without any morphologic evidence of an inflammatory reaction during the induction period. With the discovery of carcinogenic hydrocarbons and of the structural similarity between these agents and steroid hormones and cholesterol, many hypotheses were propounded on the possible alteration of physiologic secretions and constituents

into carcinogens. Further work showed no common chemical structure of carcinogenic agents, and although evidence is accumulating that repeated injections of certain tissue extracts may produce neoplasia in mice, no carcinogenic agent related to the carcinogenic hydrocarbons has been discovered in tissues up to the present. It is still possible to postulate that the numerous carcinogenic agents, including physical agents and viruses, stimulate the production by the body of a common denominator carcinogen that in turn reacts on cells and leads to malignant transformation. The only trouble with this hypothesis, as with so many others, is that there are no factual data to support it.

A more logical biochemical concept is that all carcinogenic agents, although having many other properties that are dissimilar, exert a similar physiologic or biochemical effect on tissues. For example, Warburg's observations on the altered respiratory metabolism of neoplastic tissues have been extrapolated to causal relationship: cells exposed to prolonged periods of interference with respiratory metabolism, induced by endogenous or exogenous agents, adapt themselves to the new environment and transmit this adaptation to successive generations of cells. Or the transformation is the result of constant or intermittent inhibition of cellular proliferation, an effect which was noted to be exerted by carcinogenic hydrocarbons on tissue culture or body growth. Or the agents produce a disturbance in the cellular or systemic metabolism of sulfur, or of some specific enzyme system.

One of the few rather definitely established facts about cancer in animals and man is that it is not a bacterial disease. Infestation with larger parasites is definitely connected with several types of carcinogenesis in rats and in man, but such parasites always have been interpreted as carriers of smaller causative agents or producers of chemical substances more directly associated with the neoplastic process.

The virus theory of cancer attracted many adherents following the discoveries of Rous but then fell into disfavor. Recent data on the Shope papilloma virus and on the milk agent of mice incriminated viruslike entities in the genesis of two types of mammalian neoplasms, and the theory has again returned to prominence. The theory postulates that viruses are not merely the causative or extrinsic stimuli for the initiation of cancer, which would place them among chemical and physical agents known to be involved in the induction of certain neoplasms, but that they are an integral portion of the cancerization process of the cell. It is suggested that all other agents stimulate a more or less ubiquitous virus, occurring in a latent state within cells, which then reproduces within the cell and stimulates the reproduction of the cell. The virus being a self-reproducing entity, is thus transmitted through subsequent generations of the cell. Cancer, according to this hypothesis, is an infectious process and the result of a virus-cell symbiosis. Although there is no doubt that several types of neoplasia are associated with a viruslike agent, the wider extensions of the theory, as well as the question as to whether all neoplasms are due to a viruslike agent, are matters of speculation.

Most theories of cancer assume that the essential feature of neoplasia, autonomous growth, is a manifestation of a stimulated growth process, that is, something is added to the cell which forces it to divide, to invade, and to destroy. The extraordinary property of tissue cells is not that they occasionally assume neoplastic properties but that in most instances they "know" exactly when to stop growth following injury, during regeneration, and during embryonic development. Rather than a stimulation cancer can be considered as the loss or absence of certain inhibiting substances, perhaps in some way related to the tissue organizers of Spemann.

There is adequate proof that genetic background influences susceptibility to neoplastic reactions. Neoplasms are characters and not gene factors, and susceptibility to neoplasms is expressed in degree. The view that cancer is a single Mendelian factor, either dominant or recessive, is no longer tenable.

The continued reproduction of cells in neoplasia and the transmission of characters from one cell to another for an almost limitless number of generations are in agreement with the view that cancer is a manifestation of a genetic difference from normal cells or a genetic alteration of normal cells. The embryonal theories assume that these genetically different cells, possibly merely insufficiently differentiated cells, exist in the tissues but are held in abeyance until certain stimuli cause them to proliferate or, perhaps, reduce the counterbalancing inhibiting effect of normal cells and reactions. In order to assume that normal cells can acquire neoplastic properties through genetic processes, the mechanism of mutation is necessary. The localized nature of most forms of carcinogenesis and the recent accumulating evidence that some neoplasms are not only a local reaction but may also be elicited in tissue culture strengthen the concept that if the neoplastic reaction is a mutation, it does not involve the whole organism or the germ and therefore must be a somatic mutation. It must be admitted that the somatic mutation concept is in accord with the main properties of neoplastic cells and that the cytoplasmic transmission of self-reproducing entities, whether viruses or altered cytoplasmic macromolecular complexes containing ribose nucleoprotein, is the only nongenetic explanation that at present seems feasible as an alternative.

None of the theories of cancer furnishes a wholly adequate explanation of the neoplastic reaction and none is in thorough accord with all the clinical and experimental data that have been laboriously gathered during the past century. At the same time despite all that has been written in defense or in attack of one or another of these concepts, they are not entirely contradictory or exclusive. Two questions are involved in the genesis of cancer: (1) The extrinsic or causal genesis which concerns the inciting factors leading up to the development of the neoplastic state, and (2) the intrinsic or formal genesis, or the factors responsible for the nature of the cancer cell. The distinction of these two phases is far from academic. Cancer must be a reaction of the body, or tissues, or cells, to certain stimuli. Even if it is admitted that the reaction pattern is similar in the intrinsic phase leading to neoplasia this does not imply that the extrinsic factors initiating the reaction must be identical or

closely similar. And the discovery of extrinsic causes of cancer does not explain how or why the cells or tissues alter from the normal to the neoplastic.

The truth of the matter is that although there is a considerable amount of knowledge concerning the external etiologic factors and the characteristics of the established neoplastic tissue, practically nothing is known about the intermediate zone. There is almost no definite information as to what happens during the all-important phase between the introduction of the carcinogenic agents and the reaction of the tissues or cells that eventuates in frank neoplasia. Extrapolations of observations on the original and the final phase of the process into the intermediary zone soon necessitate the introduction of almost entirely hypothetical entities or processes. Furthermore, even some of the basic statements often made about the nature of the fully established neoplasms do not withstand more critical examinations. For example, it is often stated that cancer is noninfectious. It may be true that cancer is not contagious, in the commonly accepted meaning of the term as it relates to bacterial diseases, and the statement may be justified in order to reduce the layman's fear of contact with cancer, but scientifically the conclusion implied is not warranted. Again, it is often stated that in cancer the stimulus does not have to be present throughout the process, the reaction continuing after the removal or the absence of the stimulus. This is perhaps true only of the very gross external stimuli that may be applied, it is entirely unknown whether some more fundamental stimulus, such as a virus, may not be continually needed. It would be just as improper to attribute the same property to tuberculosis, for instance, simply because only a single injection of tubercle bacilli is needed to evoke gross manifestations of tuberculosis in a guinea pig weeks or months later. A third oft-repeated dictum is that cancer is an irreversible process, once cells have acquired neoplastic characteristics, they cannot revert to normal growth. This deduction, used in the mutation theories of cancer, lacks proof and may well apply only to the last, frank stage of the process.

Morphologic studies on developing tumors fail to reveal a definite stage that may be designated as the point at which normal cells become malignant. There appears to be a gradual process, initiated by the origin of a few abnormal appearing cells that gradually accumulate and form a hyperplastic lesion, which, in some cases, proceeds to break through its normal boundaries, to invade, and, finally, to metastasize. Whether the original abnormal cells are malignant from the outset and the subsequent stages are merely a quantitative increase in their number or whether the cells themselves undergo further changes in the direction of increased autonomy is unknown. If the former view is correct, the differentiation between benign and malignant tumors is rather artificial and represents the noninvasive and invasive stages of the same process, if the latter view is substantiated by further investigations, then the transition from normal to malignant is not sudden but accumulative and gradual.

It is only too evident in the critical examination of any all-inclusive theory of cancer at this stage of knowledge, that most authors accept some particular theory and interpret the factual data in the light of this theory. If the virus

theory or the mutation theory is accepted as a postulate, many findings can be fitted satisfactorily and fortified by analogy to other processes. Such methods have a definite place in science as long as they do not interfere with scientific endeavor on an operational rather than a theoretical level, in other words, as long as they are regarded only as working hypotheses and actual experimentation is not limited to proving the particular concept.

There are at least 250 chemicals of unrelated type of structure and physiologic activity, several forms of physical energy, and several types of viruses and parasites that are known to be carcinogenic. That is, exposure of certain susceptible tissues to these agents leads in at least a certain percentage of cases, to the eventual development of neoplasia at either the site of application or at distant sites. Apparently any cell, or, more likely, any group of cells that has the property of growth and reproduction can, under proper stimulation become the ancestor of cells that manifest characteristics associated with neoplasia.

Etiologically cancer can be viewed as a group of diseases rather than as a single disease entity. All experimental work that has delved into the problem emphasizes that the neoplastic reaction is the end result of an intricate interplay of a number of complex factors and that these factors are different for different types of tumors.

In the examination of established factors that influence the genesis of specific tumors, it becomes apparent that these are not only not the same for all tumors, but also may be diametrically opposite.

The most thorough analysis of factors involved in carcinogenesis has been achieved with mammary tumors in mice. It has been shown that at least four sets of factors are involved: the genetic, the hormonal, the milk influence, and the influence of other environmental factors such as diet. The presence of the genetic, hormonal and milk factors leads to the appearance of mammary tumors, but the relative weakness of one of the factors can be overcome by increasing the other factors, and evidence is accumulating that these factors can be replaced by others: for example, the milk factor by carcinogenic hydrocarbon or the estrogens by adrenocortical secretions.

In Table III an attempt is made to outline some of the factors involved in the genesis of a few most extensively studied tumors. Two facts stand out: (1) the differences in the factors known to be involved even in these few tumors, and (2) the numerous question marks which represent absence of conclusive investigation. The inevitable conclusions are that neoplastic diseases are a most complex biologic problem and that perhaps our approach to the problem has been directed too greatly to encompass the whole field of neoplasms rather than to give adequate emphasis to specific neoplasms.

For a pragmatic approach that stimulates most and hinders least our acquisition of knowledge concerning neoplastic diseases it is safer to forego generalizations. Our knowledge of cancer simply has not reached the stage of analysis requiring consideration of different types of cancer as different entities which is a prerequisite for synthesis. To attempt to synthesize knowledge of cancer under one etiologic theory before considerably more data are avail-

TABLE III. SOME FACTORS INVOLVED IN THE GENESIS OF SOME EXPERIMENTAL NEOPLASMS

NEOPLASMS	SPECIES	GENETIC INFLUENCE					DIETARY INFLUENCE
		CHROMOSOMAL	EXTRA-CHROMOSOMAL	MILK INFLUENCE	HORMONAL INFLUENCE		
Mammary adenocarcinoma	Mice	-	-	-	(Limited to females)	-	(Deficient diet underfeeding decreases incidence)
Pulmonary adenocarcinoma	-do-	-	-	-	-	-	-
Hepatoma induced by benzodioxin	-do-	-	?	-	-	?	?
Leukemia	-do-	-	-	-?	(More in females)	-	-
Subcutaneous sarcoma induced with roentgen rays	-do-	-	-	-	-	-	(Underfeeding decreases incidence)
Mammary fibroadenoma	Rats	-	?	-	(More in males)	-	(Underfeeding decreases incidence)
Hepatoma induced by aflatoxin	-do-	?	?	?	(Limited to females)	?	?
Mammary carcinoma	Rabbits	-	-?	-	+++	-	(Deficient diet increases incidence)
					(Limited to females)		

- Mild influence    ++ moderate influence    +++ strong influence    \* not recorded  
 - - - - - reported present or absent but indefinite

able to reject findings on one group of neoplasms because they are not applicable to others and to place primary importance on the few general criteria that have been given too often erroneously as typifying all neoplasms can be only unnecessary and artificial barriers in the pursuit of experimental work. Until many types of neoplasia are understood much more clearly than they are now and until the observations have been checked and rechecked by sound scientific work all inclusive theories of cancer must be classed by the research worker as unproved. This is not a rejection of such hypotheses but an acquiescence in our incomplete state of knowledge which demands actual experimentation at the laboratory bench rather than discussion in a machine.

Cancer research must advance on two broad fronts: (1) the study of carcinogenesis which may eventually lead to the prevention of neoplastic diseases and (2) the study of tumor growth which may be the basis of therapy. In the writer's opinion it is desirable at this stage of the problem to orient such studies more along the lines of specific neoplastic diseases rather than along the lines of scientific disciplines. Moreover if cancer is one disease the clarification of one type should be easily applicable to the whole field. Particular emphasis is necessary on the intermediary phases of the process between the introduction of the carcinogenic stimulus and the appearance of the frank neoplasm. These types of approach require an accentuated group

effort in which many scientific disciplines are strongly represented and in which the competent cancer research workers have an adequately compensated and assured status. The most important elements necessary for continued progress, however, are conscientious scientific effort and patience, slow and exasperating though the work may occasionally seem.

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## Chapter III

### PATHOLOGY OF CANCER

#### THE PATHOLOGIST'S RESPONSIBILITY

The pathologist has definite limitations of responsibility. He is responsible for the proper handling of tissue after it reaches his laboratory. He, however, can diagnose only the tissue submitted. If this tissue is poorly selected and does not reveal tumor, it is not his responsibility. If a negative report is given, then a false sense of security may be engendered by the physician who submitted the inadequate material. The pathologist will give the best diagnosis who not only has adequate material, but has all the pertinent data regarding the patient on whom the biopsy has been made. He should know the name, the age, the sex of the patient, the duration of the disease, the exact location of the lesion, its size in relation to other organs, and all details of previous treatment (surgical or radiotherapeutic). The hospital chart should be available for consultation, the patient examined if necessary, and the results of other laboratory examinations available for inspection. There are definite limitations to diagnosis on the basis of morphology. With all this information and with clinical experience in the evolution and biologic behavior of tumors, the chances of a correct diagnosis will be heightened.

#### BIOPSY

It is imperative that pathologic verification of malignant tumors be present before any therapy for them is instituted. Grievous errors can be made if this is not done. An apparently typical epithelioma may be treated by radiotherapy and continue to increase in size instead of regressing. Biopsy may then show a melanocarcinoma which is notoriously refractory to radiation therapy. Such delay may result in dissemination taking place before a correct diagnosis is made. Lesions thought to be inflammatory may instead be malignant. A lesion treated for syphilis may later prove to be a squamous-cell carcinoma. On the other hand, lesions thought to be malignant may, in truth, only be inflammatory. This can happen in indolent ulcers of the leg actually caused by vascular changes or even syphilis. Some of the hyperkeratotic lesions of the lip look like epidermoid carcinoma and biopsy will show only marked chronic inflammation. Fat necrosis of the breast with its firmness and adherence to the skin has admittedly been mistaken for typical carcinoma and radical mastectomy been done. If the patient has a basal-cell carcinoma rather than a squamous carcinoma, then this will be of value in follow-up, for basal-cell carcinomas practically never metastasize. These examples serve only to emphasize why biopsy should always be compulsory.

**Dangers of Biopsy**—Formal biopsy entails little danger for the vast majority of tumors. The risk of infection, bleeding, or spread of the neoplasm is minimal. Carcinoma of the breast is one tumor about which it has been said

that metastases occur if biopsy is done. We have never had any such experience, and evaluation of one series showed no relation in prognosis between those examined by biopsy before operation and those diagnosed at operation (Greenough). It has never been demonstrated that skin biopsies cause spread with the possible exception of the melanocarcinoma. It is probably better to excise this highly malignant tumor widely, although we have never seen any proved spread caused by its biopsy. We do not usually formally incise bone tumors but in most instances have obtained material by aspiration rather than by formal biopsy. When aspiration is inconclusive, surgical biopsy is indicated after tourniquet application. Frozen section is then done and the biopsy wound closed in layers without drainage or packing.

**Techniques**—In extremely vascular tumors, preparation should be made to control any bleeding which may ensue, and the endotherm knife probably should be used in order to avoid hemorrhage. This knife, unfortunately, dehydrates and chars tissue and thus makes material unsatisfactory for histologic interpretation.

The techniques of obtaining a biopsy vary naturally with the location of the primary lesion. There are certain obstacles to securing specimens and it should be emphasized and remembered that *only tissue submitted will be examined and diagnosed*. It is up to the clinician to choose a representative area for biopsy. Accessibility for biopsy of such lesions varies. Skin lesions should be taken thinly and deeply rather than broadly and superficially. It is best to take a biopsy from the margin of the tumor in order that both abnormal and normal tissue be obtained in the section since if it is taken from an area of central ulceration, there may be no tumor or only necrotic tumor present. If the biopsy is not carried deep enough, definite invasion of the base may be missed. Also, if the biopsy is cut tangentially, microscopically it may be mistaken for carcinoma because of the bizarre pattern revealed.

In the very friable tumors, grasping forceps such as the Gavford can be used and this biopsy should be taken from the cleanest zone near the tumor. It is preferable to introduce both branches of the open forceps into the tumor and then close and withdraw it. The cutting forceps (Faure) have their best indications for very firm or nodular tumors such as those which arise from the cervix or tongue. At times several biopsies from different areas will be necessary. It is important to know, however, that epidermoid carcinoma may originate within the cervical canal and external biopsy may be negative. Tumors within the oral cavity are often troublesome and as in the lip biopsy should be deep. For malignant tumors of the nasopharynx special instruments are needed and repeated biopsies are often necessary for positive results.

Incision biopsies are necessary in many instances where aspiration biopsy has yielded insufficient material or is not indicated for reasons which will be elaborated upon later. Incisional biopsy should be done on all tumors easily accessible with ulcerated surfaces such as skin lip tongue and alveolar ridge. For tumors of the breast, soft tissue and bone many times the diagnosis is difficult and it is imperative that material be obtained from the area where pathology is most likely to be demonstrated. Adequate material must be

## Chapter III

### PATHOLOGY OF CANCER

#### THE PATHOLOGIST'S RESPONSIBILITY

The pathologist has definite duties of responsibility. He is responsible for the proper handling of tissue after it reaches his laboratory. He however is responsible only for tissue submitted. If this tissue is poorly selected and does not reveal the disease, it is his responsibility. If a negative report is given, he is in the case of security, not to be engendered by the physician who submitted the material. The pathologist will give the best diagnosis possible. His department has all the pertinent data regarding the patient, and the biopsy has been made. He should know the name, age, sex, extent of disease, the duration of the disease, the exact location of the disease, relation to other organs, and all details of previous therapy. The hospital chart should be available for consultation, or prepared if necessary, and the results of therapy should be made available for inspection. There are definite standards of gross pathology and morphology. With all this information the pathologist can determine the evolution and biologic behavior of tumors, and a correct diagnosis will be heightened.

#### BIOPSY

It is surprising that a pathologic verification of malignant tumors be present in only one out of four biopsies instituted. Grievous errors can be made if this is not done. An apparently typical epidermioma may be treated by radiotherapy, and continue to increase in size instead of regressing. Biopsy may establish a melanoma which is notoriously refractory to radiation therapy. Such delays may result in dissemination taking place before a correct diagnosis is made. Lesions thought to be inflammatory may instead be malignant. A lesion treated for syphilis may later prove to be a squamous-cell carcinoma. On the other hand lesions thought to be malignant may, in truth, only be inflammatory. This can happen in indolent ulcers of the leg actually caused by vascular changes or even syphilis. Some of the hyperkeratotic lesions of the lip look like epidermoid carcinoma and biopsy will show only marked chronic inflammation. Fat necrosis of the breast with its firmness and adherence to the skin has admittedly been mistaken for typical carcinoma and radical mastectomy been done. If the patient has a basal-cell carcinoma rather than a squamous carcinoma then this will be of value in follow-up, for basal-cell carcinomas practically never metastasize. These examples serve only to emphasize why biopsy should always be compulsory.

**Dangers of Biopsy**—Formal biopsy entails little danger for the vast majority of tumors. The risk of infection, bleeding, or spread of the neoplasm is minimal. Carcinoma of the breast is one tumor about which it has been said

that metastases occur if biopsy is done. We have never had any such experience, and evaluation of one series showed no relation in prognosis between those examined by biopsy before operation and those diagnosed at operation (Greenough). It has never been demonstrated that skin biopsies cause spread with the possible exception of the melanocarcinoma. It is probably better to excise this highly malignant tumor widely, although we have never seen any proved spread caused by its biopsy. We do not usually formally incise bone tumors but in most instances have obtained material by aspiration rather than by formal biopsy. When aspiration is inconclusive surgical biopsy is indicated after tourniquet application. Frozen section is then done and the biopsy wound closed in layers without drainage or packing.

**Techniques**—In extremely vascular tumors, preparation should be made to control any bleeding which may ensue and the endotherm knife probably should be used in order to avoid hemorrhage. This knife, unfortunately, dehydrates and chars tissue and thus makes material unsatisfactory for histologic interpretation.

The techniques of obtaining a biopsy vary naturally with the location of the primary lesion. There are certain obstacles to securing specimens and it should be emphasized and remembered that *only tissue submitted will be examined and diagnosed*. It is up to the clinician to choose a representative area for biopsy. Accessibility for biopsy of such lesions varies. Skin lesions should be taken thinly and deeply rather than broadly and superficially. It is best to take a biopsy from the margin of the tumor in order that both abnormal and normal tissue be obtained in the section since if it is taken from an area of central ulceration, there may be no tumor or only necrotic tumor present. If the biopsy is not carried deep enough, definite invasion of the base may be missed. Also if the biopsy is cut tangentially microscopically it may be mistaken for carcinoma because of the bizarre pattern revealed.

In the very friable tumors grasping forceps such as the Gaylor can be used and this biopsy should be taken from the clearest zone near the tumor. It is preferable to introduce both branches of the open forceps into the tumor and then close and withdraw it. The cutting forceps (Fraure) have their best indications for very firm or nodular tumors such as those which arise from the cervix or tongue. At times several biopsies from different areas will be necessary. It is important to know, however, that epidermoid carcinoma may originate within the cervical canal and external biopsy may be negative. Tumors within the oral cavity are often troublesome and as in the lip biopsy should be deep. For malignant tumors of the nasopharynx special instruments are needed and repeated biopsies are often necessary for positive results.

Incision biopsies are necessary in many instances where aspiration biopsy has yielded insufficient material or is not indicated for reasons which will be elaborated upon later. Incisional biopsy should be done on all tumors easily accessible with ulcerated surfaces such as skin, lip, tongue and alveolar ridge. For tumors of the breast soft tissue and bone, many times the diagnosis is difficult and it is imperative that material be obtained from the area where pathology is most likely to be demonstrated. Adequate material must be

obtained so that more complete study by special stains can be made. Incisional biopsy on breast tumors should be done with a sharp scalpel under scrupulous surgical technique so that infection can be minimized. When the tumor is exposed it should be handled very delicately so that spread will be avoided.

**Biopsy of Lymph Nodes**—The pathologic changes found in lymph nodes are often confusing. It is therefore extremely important that entire nodes, whenever possible be obtained and that they be carefully fixed and meticulously stained. If generalized lymphadenopathy is present when a node is to be removed the inguinal nodes although easily accessible are almost invariably complicated by infection. Consequently the pathology found there may be confusing and some other location should be chosen. It is the rule to remove nodes in the operating room for the removal of the supraclavicular or axillary nodes may take on the aspect of a major surgical procedure. Lymph nodes which feel superficial may actually be deep and elusive.

**Biopsy of Curettings**—Curettings are best handled not by frozen section, but by proper fixation and careful staining.

**Endoscopic Specimens**—Endoscopic specimens are often small and these small specimens like others obtained in the operating room should be quickly placed in fixative before dehydration occurs. Bronchoscopic, esophagogastroscopic, cystoscopic and proctoscopic examinations may be necessary to obtain biopsies from bronchus, esophagus, upper stomach, rectum, sigmoid and bladder. Needless to say, not only is special technical training necessary to perform these procedures, but considerable experience is essential in order that biopsies be done in the proper area. Exploratory operations such as an exploratory laparotomy or a thoracotomy may also be necessary to obtain tissue.

## FIXATION OF SPECIMENS

It is probably best to put sections from tumors into Zenker's acetic or Zenker's formal solution for in this fixative most of the special stains required to diagnose some of the more rare tumors can be made. The fixative 10 per cent formalin has the disadvantage that while it is satisfactory for the run of mill pathologist, unusual tumors fixed in formalin cannot be stained by several of the more important differential stains. Portions of rare tumors should be put into 10 per cent formalin for fat stains or the dopa reaction, into 25 per cent chloral hydrate for nerve stains, into 95 per cent alcohol for phosphatase and into 100 per cent alcohol for glycogen and mucin stains. This fixation must be done when the specimen is fresh. Paraffin sections are imperative for the preparation of proper slides. It is true that in the most skilled hands celloidin sections or even frozen sections can be used with some success. Both of these methods were used in the past because they were speedy and time-saving. However, this is no longer true for with a Technicon, Zenker's fixed tissue and paraffin sections can be prepared in less than twenty-four hours.

## STAINING METHODS

The conventional stain hematoxylin and eosin, is probably the most satisfactory routine stain for a surgical pathology department. This stain is technically easy and technicians of even little experience can make good slides.

under proper direction. This stain is also the one used in most pathology departments for teaching purposes, and therefore the house staff and visiting physicians are most familiar with it. Other special stains require special techniques and special staining. The fibroglia fibrils of fibrosarcoma are revealed with accuracy with a phosphotungstic acid and hematoxylin stain. The fat globules within a liposarcoma are shown with clarity with a sudan IV stain. At times an iron stain may be of differential importance in deciding whether or not a tumor is a melanocarcinoma.

## SPECIALIZED PROCEDURES

### Aspiration Biopsy

The attitude toward aspiration biopsy varies in application from absolute rejection to overenthusiasm and overapplication of the procedure. We feel that it has definite value in certain specific instances, that it is simple, rapid, and harmless, and that it is a valuable adjunct to diagnosis. The technique is simple, requiring only a large syringe, usually 20 or 50 cc., an 18 gauge needle 5 to 12 cm. long, a Bard Parker knife (No. 11), and novocain. The needle must be sharp, for if the tumor contains a great deal of fibrous tissue, the needle should be able to cut out a small wedge of tumor. The skin is cut with the knife in order to avoid the carrying in of infection or squamous epithelium. The needle is then inserted into the tumor, *moved around during the procedure*, while vacuum is constantly kept in the syringe. *The material thus obtained is placed on filter paper in the usual fixative and treated as a paraffin section.* This is in contradistinction to the method of smearing the material and then immediately staining it. This smear method, while it can be used by very well trained pathologists, does have several disadvantages. In the first place, all architectural detail is of necessity lost. Consequently, the diagnosis must be made on the basis of cellular detail alone. Therefore, we use the first method because in reality it provides a small biopsy which returns architectural detail and the normal relationships and differs from the usual biopsy only in size.

**Indications and Limitations**—There must be at all times sympathetic co-operation between the surgeon and the pathologist (Stewart). Aspiration biopsy is *restricted to hospitals where men experienced in the technique and interpretation are available*. In no other biopsy is it so necessary for the pathologist to have an intimate knowledge of the clinical history and physical findings of a case to be aspirated. It might be wise for him at times to question and examine the patient. The palpation of the tumor with the needle may reveal the thickness of a capsule, the consistency of the tumor, the presence of bone or the depth of the lesion.

There is no doubt that while aspiration biopsy has its place, it should not be extended to cover all situations. Its use should be limited to those cases in which formal biopsy is troublesome or impossible or where it can perhaps be substituted for a major surgical procedure such as a thoracotomy or an exploratory laparotomy. For instance it may be misleading to aspirate breast tumors when formal biopsy or exploration can be done so simply. Aspiration

of metastatic nodules in the liver, soft tissue masses, particularly sarcomas, and even bone tumors can be done easily and the complication of leaving tumor implants along the tract of the aspirating needle has never occurred in our experience

**LYMPH NODES**—A formal biopsy of nodes in lymphomas should certainly be done, for the diagnosis is difficult enough with an incisional biopsy and would be impossible with an aspirated specimen. It is most valuable in diagnosing other lymph node lesions, particularly those suspected of containing carcinoma (Fig 5). In practically all of these instances the primary will already have been diagnosed. Difficulty in aspirating inguinal, cervical, and axillary nodes increases in the order listed. Inguinal nodes are easily found and this biopsy is of particular value in aged patients with carcinoma of the penis or vulva on whom a radical groin dissection is contemplated. Cervical nodes are a bit harder to locate, but the biopsy is advantageous for determining whether accessible ones contain tumor, particularly when there is a primary lesion within the oral cavity. If an enlarged cervical node is considered metastatic, it is imperative that proof of tumor within the node be shown so that treatment by radiotherapy may be given credit if cure is effected. And vice versa, if the node is only inflammatory, it is still just as important that proof be obtained. The axillary lymph nodes are located in a large volume of fat and loose tissue and it is often troublesome to isolate small nodes in this area.

**BREAST**—Perhaps in certain rare instances where the carcinoma of the breast is far advanced and no treatment or palliative x-ray therapy is contemplated, aspiration might be done merely for obtaining tissue for the record. For an incisional biopsy of the breast, the sharp scalpel is preferable, for tissue can be removed undamaged and properly fixed and the topography is undisturbed. In some instances, cells thought to be malignant can be aspirated from a breast tumor which is entirely benign, such as duct hyperplasia or papillary cystadenoma. Usually the determination of the malignancy of a papillary cystadenoma depends on multiple sections through the capsule. Only infrequently are well-differentiated tumor cells confined to ducts, and doubtless the acinar type of carcinoma could not be recognized on aspiration biopsy. It can be argued that if the biopsy is negative, then this is of no significance, but in some instances a false sense of security may result from a negative biopsy. In any small tumors of the breast where there is a reasonable doubt of carcinoma, exploration with frozen section would seem more practical. Small tumors of the breast can easily be by-passed in aspiration and material from a cyst close by perhaps be accepted. The comedo type of carcinoma is recognized by its topography rather than by the individual cells, which are quite regular (Haagensen). Some of the atypical cystic mastitis lesions can be easily misdiagnosed on aspiration.

**LUNGS**—The aspiration of peripherally placed lung tumors, which make up approximately 25 per cent of all carcinomas, is attended with no difficulty and, in our experience and that of the Memorial Hospital staff, with no complications. Many thoracic surgeons are opposed to doing aspiration biopsies

on lung tumors, for they say that whether the aspiration biopsy is negative or positive, exploratory thoriotomy will be done. However, the problem is much more complicated than this. Certainly, if a diagnosis of a benign tumor such as a neurofibroma is made, the thoracic surgeon is going to alter the extent of his operation and perhaps his surgical approach. Also, if a diagnosis of some inflammatory lesion such as a tuberculoma is made, this will also alter the extent of the procedure. Furthermore, if metastatic carcinoma from a

Fig 4



Fig 5

Fig 4—Aspiration biopsy from a soft tissue recurrence of an undifferentiated osteogenic sarcoma. Note preservation of architectural pattern (moderate enlargement).

Fig 5—Aspiration biopsy of a submaxillary lymph node containing metastatic epidermoid carcinoma. The primary tumor arose from the lower lip. Note epithelial pearls (high power enlargement).



primary occult lesion of the kidney is diagnosed, this will also alter prognosis and perhaps will obviate thoracotomy. The thoracic surgeon who does not have the benefit of aspiration biopsy has to make a diagnosis on the basis of palpation, which will tell him but little. Very few thoracic surgeons will ever cut into the lesion which they are intending to resect because of the dangers of infection, so that frozen section diagnosis cannot be resorted to. The danger of implanting tumor in the needle tract has been reported three times in the literature (Ochsner, Dolley). One of these cases had tumor growing apparently within pleural fluid and consequently the chance of needle tract tumor implant was greatly increased (Dolley). Even if this complication occurred once in one thousand times is it not true that the information gained from aspiration biopsy of a peripherally placed mass in the lung is of much more value to the surgeon and patient than the risk of this rare complication?

**BONE**—When cortical bone has been destroyed and there is a pathologic lesion of bone, aspiration through this area of destruction is performed easily and adequate material is obtained (Fig. 4). It is of particular value in lesions of the mandible and antrum.

**LIVER**—Aspiration of the masses within the abdomen can also be done if some common sense is used in the selection of patients. If there is any question as to whether the intestine is firmly adherent to the liver, for example, and if danger of perforation of intestine is present, aspiration should not be attempted. However, if the patient has a nodular liver close to the abdominal wall aspiration of liver masses can be done with no difficulty. Gullman has reported on 500 aspiration biopsies and in only one instance did intraperitoneal hemorrhage take place. This was not due to a capsular tear but to puncture of the large artery. He felt that the aspiration biopsy was indispensable for the diagnosis of lesions which showed hepatic enlargement.

**Interpretation**—The interpretation of aspiration biopsy depends upon the experience of the pathologist and the cooperation which the surgeon gives to him. This interpretation will be enhanced when all available information is at hand. The diagnosis of squamous carcinoma or adenocarcinoma within lymph nodes is attended with no difficulty. In fact if broken-down keratinized material is obtained from a lymph node, there can be no doubt that this represents metastatic squamous carcinoma. It is usually impossible to make a diagnosis of Hodgkin's disease or lymphosarcoma or related entities, because in these instances larger biopsies are of more value. The adenocarcinoma within a lymph node, for example, of an inguinal lymph node, representing metastasis from an adenocarcinoma of the endometrium presents no difficulty. Soft tissue lesions such as sarcoma present considerable difficulty at times, and it is very frequently impossible to classify them exactly, although one is usually able to state that it is a sarcoma. Aspiration of lesions within bone presents considerable difficulty in some instances. Usually the pathologist is able to state that it is a tumor or an inflammatory lesion, and very frequently he is able to classify the tumor exactly. Metastatic lesions within bone may cause considerable difficulty. In both soft tissue sarcomas and bone tumors incisional biopsy may be necessary for exact classification.

### Examination of Sputa and Bronchoscopic Aspiration Specimens

When bronchogenic carcinoma is suspected, the sputa may be examined for malignant cells. Wandall demonstrated the value of this procedure in cases where the lesion was peripherally placed (inaccessible to bronchoscopy). Herbut recently emphasized that direct aspiration from a peripheral bronchus suspected of harboring a bronchogenic carcinoma is the most fruitful way of examining for carcinoma cells. He feels that examination of the sputa is often difficult. He believes that by staining material obtained by Papanicolaou's method a certain number of early cases of carcinoma of the bronchus not accessible by bronchoscope or aspiration biopsy will be diagnosed. In his first series he had seven patients with negative endoscopic examination and with positive secretions. When such secretions are positive, then the diagnosis is assured. In practically all cases tumor cells will be obtained. In twenty-three patients with proved carcinoma of the bronchus, secretions were positive in twenty-one.

### Urinary Sediments

Papanicolaou has extended his procedure to include the study of urinary sediment. This has been helpful in diagnosing certain tumors of the bladder or kidney which have been difficult to diagnose by conventional methods. This procedure has a limited application but in certain specific instances, particularly in early carcinomas of the kidney, will prove valuable if possible. One carcinoma of the bladder occurring in a diverticulum was diagnosed by this method. We have also been interested in this method and have centrifuged specimens of urine obtained either by catheterization of the bladder or of one ureter, and by handling this in the same manner that pleural or ascitic fluids are handled in a few instances diagnosis has been made.

### Vaginal Smear Examination

The diagnosis of carcinoma from the vaginal smear has been popularized by Papanicolaou. It should be emphasized, however, that the interpretation of such smears requires special training and painstaking technique and that false negatives can occur. It is very infrequent that smear diagnosis will be more effective than formal biopsy or dilatation and curettage. This procedure will probably find its greatest value as a screening test for diagnosing the existence of cervical or endometrial carcinoma in large groups of women who have no symptoms (Gates).

### Examination of Pleural and Peritoneal Fluids

When fluid is present in either the pleural or peritoneal cavity it may contain neoplastic cells. This fluid can be aspirated and paraffin sections made. The chances of a positive diagnosis from ascitic fluid are better than fluid from the pleural cavity. A diagnosis of cancer should never be made on pleural or ascitic fluid unless there are fragments of tumor present containing definite nuclei or specific masses of atypical cells (Schlesinger). It is very dangerous to attempt a diagnosis on the basis of the relation of the

nucleus to the nucleolus a single cell or the presence of a rare mitotic figure. Mesothelial cells can arrange themselves in pseudogland and cause perplexity. On the other hand, errors of omission may be made even when a tumor is present in the pleura or peritoneum. This mistake occurs when tumor cells are few in number, absent in the fluid, or difficult to recognize. Fluids from the pleural and peritoneal cavities can be diagnosed after sedimentation in the following manner:

*Method*—Measure and take the specific gravity of the fluid. If the amount of fluid is small, centrifuge at once. If it is large, add 10 per cent formalin to make a 10 per cent solution. Allow the cellular elements to settle for several hours. Then decant the supernatant fluids and centrifuge the residue for thirty minutes at 500 revolutions per minute. If the residue has not formed a firm mass, pour off the supernatant fluid again and fill the tubes with 10 per cent formalin and centrifuge for thirty minutes. Remove mass from the tubes and treat as a piece of tissue. Imbed in paraffin and stain the usual way.

It is best to cut the block in various planes and at different levels so that cells from all areas may be examined.

### Frozen Section

Frozen section diagnosis is a rapid method of taking fresh tissue and cutting and staining it for microscopic examination so that a number of slides can be looked at in a short period of time. The following technique is used in our hospital:

The tissue is frozen with carbon dioxide and cut with a microtome at about from 20 to 40 micra.

The sections of mixed tissue are placed on a slide and stained with 0.5 per cent solution of thionin in 20 per cent alcohol for thirty seconds to one minute, according to the thickness of the sections. They are then washed in water and mounted on a slide (from water). The section is covered with glycerin or glycerin jelly and a cover slip. Results: nuclei blue to purple, collagen, reddish and elastin, light green. This is a polychrome stain which colors the epithelial cells blue and the connective tissue pink.

Frozen section should be used as sparingly as possible, for there is no doubt that paraffin sections are far superior. However, there are certain instances where, if a decision can be made, the surgeon can save time and either proceed with the operation or make a definite decision that it is not indicated. It probably has its greatest value in tumors of the breast. In most breast tumors the gross diagnosis can easily be made. However, there are a certain few in which, at the operating table, doubt exists as to whether they represent carcinoma or not. In these instances frozen section should be done.

In the excision of squamous carcinoma of the skin because of coexisting infection it may be impossible to determine where tumor ends. Frozen section is indicated in these instances because it may determine the extent of procedure. Certain bone tumor lesions can be diagnosed by frozen section, but certainly in many instances if the lesion has not been diagnosed by aspiration biopsy then probably permanent sections will have to be made rather than frozen section. It may be of value in differentiating chronic thyroiditis from carcinoma. At the time of exploration of the abdomen for various conditions frozen section is sometimes indicated. The proof of involvement of a lymph node at some distance, for example, from a carcinoma of the stomach, may

obviate gastric resection. When to do frozen section at operation is best determined by the surgeon. This will find its indication in resolving a diagnosis between perhaps an inflammatory and a malignant condition.

In the differential diagnosis between carcinoma of the pancreas and chronic pancreatitis, where palpation or inspection are of little value because both conditions make the pancreas feel very hard, frozen section is of value. In this instance, probably frozen sections, which take a longer period of time (twenty minutes), are better. They are stained with hematoxylin and eosin. At times, when exploration of a questionable prostatic nodule is done and carcinoma can be proved by frozen section a radical operation can be immediately carried out. It obviously has little value for uterine curettings when only a limited number can be examined. It would probably be much more prudent to wait for the permanent sections. In many instances the differential diagnosis lies between hyperplasia and carcinoma of the endometrium. Hodgkin's disease and lymphosarcoma are notoriously difficult to diagnose by frozen section and the attempt probably should not be made.

The pathologist's attitude toward frozen section should be a conservative one, for in practically every instance if any doubt exists as to the proper diagnosis, no harm is done by returning the patient to the floor and waiting for permanent sections. From the standpoint of the surgeon, the pathologist can give a much better diagnosis if he has all clinical information available before frozen section is done. It is often also helpful for him to examine the patient before this procedure.

### Excisions

Certain lesions, particularly those of the skin, are so located and of such a size that complete removal is possible. When these specimens are submitted to the laboratory sections should be taken very carefully from three planes particularly through any area where there is question of adequate excision. Complete removal of the tumor should be carefully determined. These should be accurately marked so that if incomplete removal is demonstrated, then the probable point of recurrence can be carefully watched or re-excised. It should be pointed out that even when the sections are taken as outlined, tumor may be present in some other area not sectioned, although the chances for error are low. The normal margins around a lesion are usually adequate but not infrequently the depth is insufficient. This is commonly found in basal cell carcinomas which have a marked tendency for deep infiltration. Tumors unaccompanied by a meager connective tissue stroma may not be recognizable. In every questionable instance the excision should be deep. There are numerous other excisions particularly for skin carcinomas which are, of necessity, extensive. It is profitable to label these excisions carefully and to take sections at appropriate areas in order to determine whether the excision has been adequate.

### Tissue Culture and Hormone Studies

There are certain specialized tests in which the pathologist must be interested in the diagnosing of tumors. It is realized that the microscopic study of tumors is often not satisfactory because it is a static rather than dynamic

phenomenon Tissue culture as a method of identification of certain specific types of tumors has been proved fruitful in the hands of Murray and Stout They have been able by tissue culture methods to identify definitely such tumors as neuroblastomas, synovial sarcomas, liposarcomas, etc Greene has been an enthusiastic advocate of identification of tumors by means of tissue culture He has demonstrated that human cancer can be transferred and will grow in the anterior chamber of the guinea pig's and rabbit's eye He has used this as a method of identifying malignant neoplasms Greene believes that failure in transplanting benign tumors suggests that heterotransplantability is a characteristic property of cancer There are hormone studies which can be used with particular tumors that may be helpful in the differential diagnosis This applies specifically to testicular and ovarian tumors Some of these tests will be discussed in detail later

### GROSS DESCRIPTION OF SURGICAL SPECIMENS

The tumor should be described in relation to other structures, giving its exact size, color, and consistency All lymph nodes or large blood vessels should be found and carefully charted The blood vessels should be opened and tumor invasion looked for The diagnoses in some tumors are grossly obvious The chalky streaks of a carcinoma of the breast, the polypoid, well-delineated carcinoma of the rectum, the serous cystadenocarcinomas of the ovary with their papillary projections and cysts, and the bright yellow of the kidney carcinomas are clear on inspection Tumors which are benign are usually quite clearly differentiated from malignant tumors for they have not metastasized, and usually have a definite capsule

#### Lymph Node Metastases

The prognosis of many tumors is directly dependent upon the presence or absence of lymph node metastases Many series of cases report either the presence or the absence of spread, but seldom is it clear by what methods the nodes are proved negative If the nodes are positive microscopically there is indeed no challenge, but the group in which the nodes are stated negative should have further verification When recording information about metastatic lymph nodes, the number, distribution, and respective involvement should be diagrammatically portrayed after gross and microscopic examination of the specimen It is obviously of greater significance in carcinoma of the breast when the high point of the axilla is involved than when the low axilla alone is involved The number of involved nodes also has prognostic significance There is no doubt that if refined methods of clearing are used, large numbers of nodes will be found, Collier found an average of 30.2 in the stomach, Ginnell found an average of 52 in the rectum, and we have found an average of about 40 in neck dissections This dissection of lymph nodes from any surgical specimen is a meticulous and time-consuming procedure, but the rewards are gratifying For instance, in carcinoma of the breast it is not unusual to find that of perhaps thirty axillary nodes, only one is replaced by tumor A few negative nodes, therefore, are of much less consequence than are fifty negative nodes Frequently, very small, soft, grossly

negative lymph nodes are replaced by tumor in the same surgical specimen where there are negative large, fairly firm, homogeneous gray nodes. When infection accompanies the primary tumor, the nodes may be very hard, homogeneous, enlarged and gray on cross section but still be negative. The large obviously involved nodes show focal zones of grayish yellow tumor. The reason why some cases of carcinoma of the breast, penis, vulva, and others are not cured after operation in spite of apparent negative regional nodes may revert back to an initial examination which was not thorough. The same inaccuracy is repeated in autopsy statistics. For instance, conscientious dissection of node areas at autopsy for cancer of the bladder is usually not done and this carelessness has led to the oft repeated statement that the tumor is well localized and does not tend to metastasize.

### Blood Vessel Invasion

Blood vessel invasion is usually not noted grossly in surgical specimens with certain exceptions. It is important that certain tumors removed surgically should be examined very closely grossly for evidence of blood vessel invasion. This particularly applies to carcinoma of the thyroid and other lesions of the upper neck, kidney, and large bowel. This gross blood vessel invasion will be seen as tumor which has grown directly within the vein. This is not too unusual in carcinoma of the thyroid. In certain metastatic lesions of the neck a lymph node may break into a jugular vein and tumor may be present there. It is extremely important in tumors of the thyroid that evidence of blood vessel invasion be searched for. In kidney neoplasms the prognosis will depend on whether the renal vein is invaded. Rarely such gross blood vessel invasion will be noted in malignant tumors of the large bowel.

### MICROSCOPIC DESCRIPTION OF SURGICAL SPECIMENS

The microscopic description should be as brief as possible. Some mention should be made of its degree of differentiation. If there is evidence of blood vessel invasion or nerve sheath invasion these should be indicated for they may very well be of prognostic significance. Frequently special sections are taken to determine whether the excision has been adequate and careful statements should be made concerning them. Detailed descriptions may be necessary in rare tumors.

### DIFFERENTIATION BETWEEN BENIGN AND MALIGNANT TUMORS

The differentiation between the benign and malignant tumor is usually not difficult. A typical benign tumor is usually encapsulated and the capsule is made up of connective tissue. On section it usually reveals a rather relatively homogeneous appearance if it is made up of the same type of tissue. At times the encapsulation may be rather poorly defined, as in a lipoma. Degenerative and regressive changes in benign tumors are much less frequent than in malignant tumors. However, if the benign tumor has been present long enough, grown large enough or has had some impairment of its blood supply then changes can take place. For instance hemorrhage may occur in a lipoma, calcification in a leiomyoma of the uterus, or a necrosis in a

benign ovarian cyst with a twisted pedicle. Microscopically the pattern of these tumors is *orderly*. Individual cells all appear the same. Mitotic figures may occur in fairly rapidly growing, cellular benign tumors, and they should not be construed as evidence of malignancy. Benign tumors do not metastasize, but if they are located in a strategic position, they may cause major pathologic alterations. For instance, a large leiomyoma may partially block the ureters, resulting in kidney insufficiency. A benign tumor growing in the bronchus may result in partial occlusion of the bronchus with secondary infection in the lung and sequential changes which may lead to death.

### TRANSFORMATION OF A BENIGN TO A MALIGNANT TUMOR

It should be mentioned that at times a benign tumor may become transformed into a malignant one. Innumerable examples of this can be listed. The slumbering fibroadenoma of long duration in the breast may suddenly become manifest fibrosarcoma. Polyps of the colon are very frequently the precursors of carcinomas. Small adenomas of the kidney become carcinoma. Papillomas of the bladder eventually undergo transition to carcinoma. Benign nevi under stimulation such as cauterization or irradiation change from an innocuous to a virulent neoplasm. Such transitions will be indicated under the various organ systems.

The malignant tumor usually does not have a capsule or, if the capsule is present, it is incomplete. Grossly, extension into the surrounding tissues or gross evidence of involvement of blood vessels or contiguous lymph nodes may be observed. On section the tumor may be homogeneous and, if very cellular, grayish-yellow in color. The malignant tumor very frequently shows areas of necrosis which are manifested as yellowish zones or areas of hemorrhage, recent or old. Microscopically, the malignant tumor invariably has a *disorderly pattern*, mitotic figures may or may not be present, and if abnormal forms are seen with asymmetrical spindles or giant forms, then probability of malignancy is high. The microscopic search may reveal tumor within veins, lymphatics, or perineural sheaths. Malignant tumors metastasize, but at the time of examination some tumors still remain localized. There is no doubt that it is extremely difficult to determine whether certain tumors are benign or malignant. This is particularly true in some very well differentiated tumors of salivary gland origin in certain rectal polyps, and in some breast tumors. These borderline lesions require considerable study and much experience in tumor pathology in deciding whether they should be treated as a benign or a malignant tumor.

### CARCINOMAS

#### Epidermoid

Von Hansemann, in 1890, originated the idea of grading certain tumors and this has since been popularized by Broders. At our hospital we have given the squamous or epidermoid carcinoma only three grades, for further division seems impractical. Grade 1 epidermoid carcinoma presents very uniform cells,

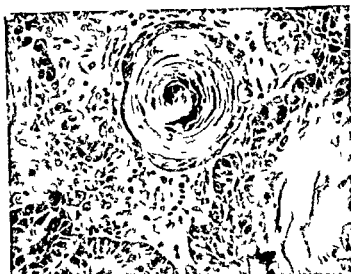


Fig 6



Fig 7



Fig 8

Fig 6—Well-differentiated epidermoid carcinoma with epithelial pearls and intercellular bridges (moderate enlargement)

Fig 7—Plexiform type epidermoid carcinoma fairly well differentiated (moderate enlargement)

Fig 8—Very undifferentiated epidermoid carcinoma showing innumerable mitotic figures and nuclear monstrosities (moderate enlargement)



many epithelial pearls, and rare or no mitotic figures (Fig 6). Grade II shows some tendency to variation in cell size and has occasional mitotic figures, few epithelial pearls, and a moderate tendency to keratinization. At times, particularly in the cervix, the epidermoid carcinoma may take a plexiform pattern (Fig 7). Grade III has a most disorderly pattern with many mitotic figures, some of which are abnormal, and practically no tendency to keratinization (Fig 8).

### Adenocarcinoma

The adenocarcinomas are also divided into three grades for the same reason. Grade I shows glands arranged in a very orderly pattern with only a few mitotic figures. The individual acini appear almost normal. Early the cells of the glands show loss of nuclear polarity and stratification of cells (Fig 9).



Fig. 9

Fig. 10

Fig. 9—Early microscopic changes of an adenocarcinoma in a gland with stratification and loss of nuclear polarity (high power enlargement).

Fig. 10—Moderately well-differentiated adenocarcinoma of the endometrium (moderate enlargement).

Grade II shows only moderate tendency to glandular formation, numerous mitotic figures, and tendency to a fairly irregular pattern (Fig 10). Grade III is so very undifferentiated that it is scarcely recognizable as an adenocarcinoma. There are numerous mitotic figures, some of which are abnormal.

### THE VALUE OF GRADING

The grading of a tumor may often be overemphasized and overrated, for it may be an unimportant feature. If, for instance, one found a Grade I

adenocarcinoma of the endometrium which had extended out to the peritoneal surface, the extension of the tumor would certainly be of much more significance than its grade. If the tumor were a small Grade III adenocarcinoma localized to the endometrium, it would still be curable and the grade would not be of too great significance. In large groups, grading is of some importance for determining end results, but in individual cases its value is diminished. The more undifferentiated the tumor the greater the incidence of metastases and the more rapid the clinical course.

There is no doubt that squamous carcinomas in certain locations such as lip, penis, vulva and skin have a tendency to be well differentiated, while those in the cervix, hypopharynx, nasopharynx, and esophagus are less differentiated. This characteristic is important when the possibility of metastases is being considered. An epidermoid carcinoma of the lower lip usually spreads only to a submaxillary or submental lymph node where it tends to grow slowly and remain localized. However, when it is undifferentiated it may spread to involve many groups of lymph nodes in the neck. In the very highly undifferentiated squamous carcinomas it can be said with some certainty that the chances of distant metastases and rapid spread of the tumor are very high. Usually these highly anaplastic carcinomas make up only a relatively small percentage of the total group. This certainly applies to carcinomas of the cervix. On the contrary, when the tumor is extremely well differentiated and a Grade I carcinoma, then it will tend to remain localized for long periods of time. Individual cases in this category have been reported from organs the source of squamous carcinomas such as the esophagus and bronchus.

## SARCOMAS

Sarcomas make up a smaller percentage of malignant tumors than the carcinomas. They arise from mesoderm and derive their names from their parent tissue. Each type, whether it be fibrosarcoma, liposarcoma, rhabdomyosarcoma, arises wherever its primary type of tissue is available. Its individual characteristics will be made the subject of a special chapter.

Lymphosarcoma is often seen first as a generalized process, but a certain unknown but increasing proportion of cases have been reported with a definite focus of origin. Regato (1939) reported that lymphosarcoma frequently arose from the region of Waldeyer's ring (nasopharynx, tonsil, base of the tongue). The second most common location is from the gastrointestinal tract, from the stomach, large bowel or small bowel. They have been reported arising from many other areas, and in some of these lymphatic tissue has been minimal in amount. The lacrimal gland (Perera), dura (Abbott), breast (Harrington), vulva (Saxton) and testis (Dockerty) are some of the zones in which lymphosarcomas have apparently been primary. In recent series of lymphosarcomas reported, an effort has been made to report how many of these were apparently of extranodal origin. In Sugarbaker and Craver's survey of 196 lymphosarcomas they felt that only about one third began in an extranodal focus and that 65 per cent of these were in head structures. It may be questioned whether lymphosarcoma ever originates in lymph nodes (Regato). This may

be a purely academic question but it is a worth-while concept to stimulate search for a primary focus when lymphosarcoma is discovered first in the lymph nodes.

The classification of lymphosarcoma has been very confusing, but it is certain that a complicated classification adds nothing to our knowledge and is of practically no significance clinically. The three types usually designated are the lymphocytic cell, reticulum cell, and giant-follicle types. The proportions of the first two types vary in reported series almost entirely on the basis of pathologic interpretation. Warren and Pincus found only 3.6 per cent reticulum cell sarcomas in 308 lymphoid tumors, using the rigid criteria of Oberling. Sugarbaker and Craver, however, reported that 94 per cent of their 196 cases fell in the reticulum cell group. In Stout's 164 cases, there were eighty-nine of the reticulum-cell variety, fifty-five of the lymphocytic-cell type, and twenty of the giant follicle type. Stout designates the lymphocytic type when the predominating tumor cell is small, slightly larger than a small lymphocyte, and uses the reticulum cell type to apply to all lymphosarcomas with cells larger than this. In both of these types enlargement of lymph nodes without fusion occurs. On section they are replaced by yellowish-gray homogeneous cellular tumor. Hemorrhage is frequent, but necrosis is unusual except in the very large nodes. Microscopically, in both the lymphocytic and reticulum cell type the architecture is erased and the tumor characteristically grows in the surrounding loose perinodal tissues. It is impossible to differentiate the node of the lymphocytic type of lymphosarcoma from that of lymphogenous leukemia without bone marrow biopsy or a typical white count. In giant follicle lymphoma there is numerical and dimensional increase of the follicles. The cells involved may be either of the lymphocytic cell or the reticulum cell type. Eventually in the advanced stages the process becomes advanced and the architecture of the lymph node is obliterated and appears like the other two main types of lymphosarcoma. In giant follicle lymphoma the spleen may be enlarged, and on section the Malpighian bodies are often seen as small gray raised tumors. In the dissemination of lymphosarcoma besides widespread lymph node involvement practically all organs can be implicated. The gastrointestinal tract, kidneys, lungs, spleen, liver, and bone are rather frequently implicated. In 164 cases reviewed by Craver, seventeen of the patients had some involvement of bone with pathologic fracture occurring five times. The most frequent sites of involvement were spine and pelvis and osteolytic changes were most prominent. About one-third of the cases of lymphosarcoma at necropsy will show pulmonary involvement (Falconer).

### THE GENERAL PROPERTIES OF MALIGNANT TUMORS

Malignant tumors have certain general properties. They are sometimes abundantly supplied with blood vessels and accordingly may give rise to profound hemorrhage when biopsy is performed. The growth of the tumor may be so rapid that the blood supply is affected and necrosis may ensue. When there is a profuse blood supply fragments of tumor cells may reach the circulating blood stream. The tumor may be very hard because of dense hyalin-

ized connective tissue stroma (breast) but the amount of stroma varies with each tumor and even in different parts of the same tumor. The cellularity of a tumor may also determine its hardness. A papillomatous tumor of the large bowel may be soft because it is made up of almost entirely epithelial cells with a very delicate connective tissue framework.

Various degenerative processes may take place within the tumor. Some tumors form mucin and consequently are very soft and gelatinous. This occurs particularly in carcinomas of the gastrointestinal tract, breast, pancreas, and gall bladder. In other instances, metastatic tumors may even form substances which will affect the host. Rarely, malignant tumors of the pancreas of islet cell origin will form insulin in their metastases. Thyroid tumors have been known to form thyroxin and primary tumors of the liver to form bile. Granulosa cell tumors of the ovary may cause feminizing changes and, conversely, cortical tumors of the suprarenal gland may initiate virilizing changes in a female.

A malignant tumor alone rarely causes death. It is rather caused by the effects of the tumor on the contiguous organs. Tumors of the oral cavity, particularly carcinoma of the tongue, pharynx, and larynx, are especially prone to interfere with deglutition and necrotic infected tumor in the oral cavity is prone to be aspirated into the respiratory tract. Carcinoma of the cervix and to a lesser degree, ovary, rectum and prostate, may obstruct the ureters and cause death from a combination of obstruction and pyelonephritis. Other tumors primarily in the gastrointestinal tract may cause intestinal obstruction, perforation or hemorrhage.

### THE CORRELATION OF MORPHOLOGIC CHANGES WITH RADIOSENSITIVITY

The pathologist is often asked by the clinician whether the tumor which he sees under the microscope is radiosensitive. The problem of radiosensitivity is mainly dealt with in the chapter on radiotherapy. The pathologist cannot determine whether any particular tumor is radiosensitive or not. It is true that certain types of tumors arising in certain locations will melt under radiation therapy. Therefore if the pathologist sees a lymphosarcoma, a lymphoepithelioma of the nasopharynx, or a seminoma, generally speaking, he might say that this tumor is radiosensitive. Usually the more undifferentiated the tumor, the more sensitive it is to radiation and if the pathologist examines a very poorly differentiated squamous carcinoma of the cervix, he might believe that this tumor would be sensitive to radiation. However, such statements would be made more on his knowledge of the evolution of that particular tumor and the radiotherapist's experience rather than on what he saw under the microscope. There is no doubt that there are many tumors which microscopically appear similar and which arise from the same organ but whose response to radiotherapy may be diametrically different. The pathologist cannot predict this. It is the pathologist's duty to describe and diagnose the tumor but it is outside of his province to determine radiosensitivity on the basis of morphologic changes.

## THE SPREAD OF TUMORS

The dissemination of neoplastic cells throughout the body is often intricate and capricious and may take diverse forms. Tumors may directly invade contiguous organs, spread by implantation, and reach distant organs by lymphatics and veins. Chance can play a pertinent role in the transfer of tumor cells. A very small tumor breaking into a large blood vessel may result in widespread metastases, while another may reach a huge size and still remain confined to its capsule. Its rate of growth, its degree of differentiation, the presence or absence of barriers to spread, and biologic and unknown factors all play a variable role in the spread of tumors.

A thorough knowledge of anatomy and a familiarity with tumor pathology are prerequisites for understanding the spread of tumors. The dissection of the tumor should be in experienced and careful hands. Autopsy examination, which is an important basis of medical learning and teaching, is more or less fruitless when the knowledge of possible metastases is limited.

### Direct Extension

Direct extension of tumor is influenced by its anatomic location. Bone, periosteum, cartilage, and dense connective tissue capsules are natural barriers against spread. To some extent muscle resists invasion, and within bone tumor grows through the periosteum with difficulty. Tumor extending around an organ may be barred from invading it by its dense capsule. Retroperitoneal tumors often grow around but do not invade the kidney. Carcinoma of the endolarynx remains localized not only because of the sparse lymphatics but because of the cartilaginous almost avascular inclosure.

### Spread by Lymphatics

By far the most noteworthy method of spread of malignant tumors is via the lymphatics, and consequently an intimate knowledge of the lymphatic system is essential for treating tumors. Some tumors metastasize early, others late, and some for no apparent reason, may remain localized for years without metastases. Spread by lymphatics is usually a matter of emboli rather than permeation. It is only when the lymph nodes are completely filled with tumor that retrograde permeation takes place. For instance, in carcinoma of the rectum the nodes proximal to the tumor are never involved unless the distal nodes are completely replaced by disease.

Carcinomas metastasize predominantly through the lymphatics. The tumor cells are first located in the peripheral sinuses (Fig 11). Tumors may grow within a node and gradually replace it, continue growing, and enlarge it to as much as 10 cm in diameter and still be confined to it (Fig 12). It is not unusual to have a metastatic lymph node, the first indication that a neoplasm exists. An enlarged axillary node may be the first suggestion of a breast carcinoma, a cervical node of a nasopharyngeal carcinoma, or an inguinal node of a melanocarcinoma.

After node replacement and enlargement, the tumor may break through the capsule and begin to grow in the surrounding loose fat and connective



Fig. 11.—Early metastatic carcinoma in the peripheral sinuses of an axillary lymph node from a primary carcinoma of the breast (low power enlargement)

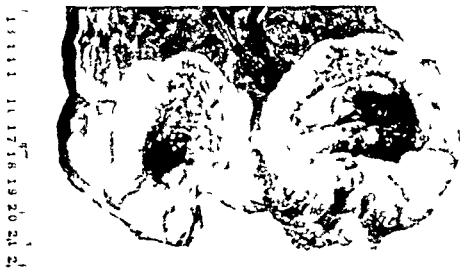


Fig. 12.—Metastatic epidermoid carcinoma within a submaxillary lymph node. This was the only nodal metastasis. Note central necrosis and fibrous capsule

tissue. This development is ominous certainly in melanocarcinomas, for we can find no cured case in which this evolution took place. In the squamous-cell carcinoma, particularly in the cervical nodes, this could be the explanation for some of the local recurrences after surgery. Carcinoma in the axillary lymph nodes, however, may grow through into the loose fat, but after a truly



Fig. 13.—Lymphangitic metastases in the lung from a carcinoma of the breast. Grayish-white areas represent tumor within the lymphatics along the path of the blood vessels. There were also metastases to hilar lymph nodes.

radical mastectomy, the chance of local recurrence seems to be small. Finally, after the tumor has grown outside of the capsule, further dissemination by direct extension, replacement of soft tissue, and invasion of the small veins can occur. The involved nodes thus become fixed. Each organ varies in the number and distribution of its lymph vessels and this variation naturally influences the extent of possible metastases from it. The thoracic duct is a

significant ally for metastasizing tumors below the diaphragm because this duct empties into large veins leading to the right side of the heart, and tumor brought to the lungs by the thoracic duct often multiplies and breaks into the pulmonary veins, reaches the left side of the heart, and thus the systemic circulation. In all autopsies for tumors located below the diaphragm the thoracic duct should be completely dissected and examined.

Perineural lymphatic sheath invasion by carcinoma is much more common than suspected and should be searched for in every tumor. It is positive proof that cancer is present. In our hospital it has been found in cancer of the prostate, rectum, breast, gall bladder, pancreas, stomach, lung, penis, tongue, salivary glands, skin, esophagus, cervix and vulva (Fig 14). In certain of

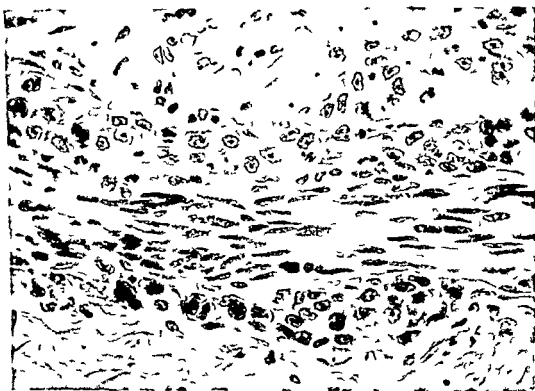


Fig 14—Perineural sheath involvement by an undifferentiated epidermoid carcinoma (high power enlargement)

the very well differentiated carcinomas of the prostate it may be the only sure sign of malignancy and may extend over a distance of several centimeters (Warren). Nerve invasion may be accompanied by intractable pain in carcinoma of the pancreas, prostate, cervix, and large bowel, invariably severe in carcinoma of the body and tail of the pancreas. After surgical removal of a carcinoma of the rectum where nerve invasion is present, the incidence of local recurrence is high (Seefeld). Worthy of mention also is that with nerve invasion lymph node metastases are usually existent and the disease advanced. Large nerves can also be involved. The facial nerve can be affected by malignant tumors of the parotid, the vagus nerve by carcinoma of the esophagus and the phrenic nerve by carcinoma of the bronchus. The recurrent laryngeal



nerve is commonly involved in carcinoma of the bronchus and even by metastatic disease from the breast

It was once an accepted truism that sarcomas metastasized only by the blood stream. Statistics now show, however, that about 5 to 10 per cent of the soft tissue sarcomas (exclusive of melanosarcoma and lymphosarcoma) metastasize by lymphatics (Warren, Willis)

### Spread by Veins

Spread of tumors through the blood stream is not as common but is just as important as spread by lymphatics (Fig 15). Tumors may grow into a vein and form a thrombus from which tumor emboli disperse. From the lung it frequently invades the pulmonary veins and thus reaches the left heart. Tumors

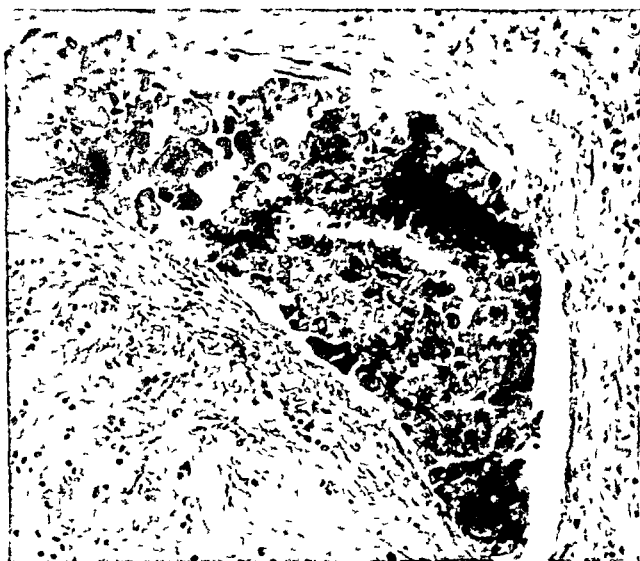


Fig 15—A cluster of carcinoma cells within a small vein. The primary tumor arose from the thyroid (low-power enlargement)

can practically destroy the wall of a vein and compress it so that thrombi form in the retarded blood stream. It can also invade the lumen and form a thrombus. This may be followed by a complete destruction of the wall and the formation of a true tumor thrombus. Metastatic disease may also invade veins. It should be emphasized that proof of vein invasion by tumor can be determined only by special histologic study. Stains to demonstrate the smooth muscle of the vein (phosphotungstic acid and hematoxylin) and its elastic tissue (Verhoeff van Gieson) are necessary, otherwise lymphatics may be mistaken for veins. The degree of tumor vascularity is also a factor inasmuch as retrograde flow through veins without valves can occur with the production of unusual metastases.

Some tumors only occasionally invade the blood vessels and this is true for lesions in the upper neck where the jugular vein can be secondarily invaded. This can occur through metastatic carcinoma, particularly from oral cavity lesions. After the tumor invades the jugular vein, it carries tumor cells to the lung through the right heart. Rather rarely, carcinoma of the breast, after it has metastasized to the axilla, can invade branches of the axillary vein and reach the right heart.

Some tumors almost exclusively metastasize by blood stream. This is partially explainable on the basis of anatomy, but in certain tumors it cannot be explained on this basis. The sarcoma group is the one which predominantly spreads through the blood stream. Chondrosarcomas in particular may propagate for long distances, for in two cases reported, a tumor thrombus extended from the femoral vein all the way to the right heart and then to the pulmonary arteries (Warren, Kosa). Carcinomas of the kidney predominantly spread through the blood stream and evidence of such spread is usually observed in the surgical specimen or it may be the first clinical manifestation. This blood vessel invasion can often be a determining factor in prognosis. Other tumors such as carcinoma of the rectum, may spread through the blood stream as well as by lymphatics, and if blood vessel invasion can be demonstrated, this may indicate the presence of liver metastases (Brown). It is also well known that carcinoma of the thyroid, as well as involving nodes, frequently involves blood stream, and the presence or absence of blood vessel invasion is important in outlook (Warren).

The trajectory of tumor emboli through the blood stream will vary somewhat according to the vein system which the tumor involves. If tumor invades the veins of the upper neck, it quickly empties into the right heart. If the tumor empties into the inferior vena cava, the emboli also reach the heart and then the lungs. After tumor reaches the lungs, it is not infrequent for this tumor to break secondarily into branches of pulmonary veins and thus be released to the systemic circulation where tumor may lodge in viscera or go to the brain. Also, if the tumor invades the portal vein system, then it ends in the liver where secondarily it may involve the veins and thus again reach the right heart.

### Vertebral Vein Plexus

Batson's studies of the vertebral vein plexus have been of great value in explaining the bizarre distributions of metastases. The vertebral vein plexus has no valves and communicates with other major vein systems. When pressure changes occur within the abdominal or pleural cavity, metastases to unexpected organs appear. This system communicates with all major vein systems. If opaque material is injected into the dorsal vein of the penis, it can reach the vertebral vein system. It is by this method certainly that carcinoma of the prostate reaches the vertebrae, pelvis, and upper ends of the femur without evidence of disease in any other organ. This pattern of spread of carcinoma of the prostate duplicates the anatomic picture of the vertebral vein plexus. When abdominal pressure is increased (cough or other means), when tumor

cells lie within veins, it is by this same system that metastatic foci in apparently unrelated organs may be explained. A cancer of the breast may be transported directly to the dorsal vertebra without evidence of disease within the lung. With cough, a carcinoma of the lung located in the area drained by the posterior bronchial vein may metastasize through this vein into the vertebral vein plexus and thence to the brain.

### Spread by Arteries

Although tumor often grows in the nodes along the aorta, it rarely invades it. In rare instances it may involve the adventitia, but because of the barrier of elastic tissue and smooth muscle it does not penetrate the media. Carcinoma of the midesophagus which is firmly fixed to the aorta can, at times ulcerate into its lumen.

### Spread by Implantation

In a few tumors, particularly those arising in the ovary, the favorite method of spread is by implantation. The pseudomucinous cystadenocarcinoma may fill the entire abdomen and grow luxuriantly on the peritoneum. With further growth it tends to invade contiguous structures. It is not unusual to have tumor recurrence appear in a surgical wound even many years after a removal of a pseudomucinous lesion of the ovary. The serous cystadenocarcinoma of the ovary also implants itself on the peritoneal surface and in some instances following surgery the satellite nodules regress spontaneously. Neoplasms associated with mucin production primary in the pancreas, stomach, and gall bladder may implant on the surface of the bowel, enucleate, invade, compress, and cause symptoms suggesting primary gastrointestinal malignancy. These implants customarily are most prominent in the pelvic peritoneum. In all surgical procedures pertaining to carcinoma, particularly of the breast, care should be taken to avoid local implantation of tumor. In rare instances fragments of tumor within the oral cavity may break away and implant in the tracheobronchial pathways. This is conceivably the method of spread in some ameloblastomas (Schweitzer).

The practical importance of this knowledge in surgery and radiotherapy is obvious. For instance, tumors arising from the vocal cord remain localized for long periods of time mainly because the lymphatics of the endolarynx are sparse. On the other hand because of the rich lymphatic plexus of the hypopharynx in practically every instance by the time the diagnosis of tumor in that region is made dissemination has already taken place. If it is known that the subcutaneous lymphatics of both inguinal regions communicate with each other, then it can readily be understood why bilateral rather than unilateral groin dissection is indicated in a carcinoma of the vulva or penis. If it is known that there are communications between the lymphatics on one side of the aorta and those on the other, it is easily comprehended why radical dissection of lymph nodes of just one side (for carcinoma of the testicle) is of little practical value and consequently that radiations should be used and directed to both sides. If it is known that tumors of the breast located in

the inner upper quadrant may metastasize directly to the supraclavicular nodes or anterior mediastinum, then clinical attention will be given to these zones.

Most autopsies done on patients who die of malignant tumors are, for the most part, a routine procedure with none or only little attempt to find out how the particular tumor spreads. Thorough knowledge of the spread and its various manifestations is of utmost importance in doing intelligent autopsies. Willis, in his book on the spread of tumors, has eloquently proved the value of this hypothesis.

### Biologic Factors

Although metastases may be conditioned somewhat by the anatomic location of a tumor and the pathways available for its spread, there are unknown biologic factors which exist and cloud the picture of tumor dissemination. For instance, carcinoma of the prostate, breast, thyroid and kidney grow luxuriantly and commonly within bone. Skeletal and heart muscles are seldom the site of metastases and to only a slightly greater extent, are spleen, pancreas and kidney. Some tumors nevertheless apparently can grow in any organ. The best example of this is the melanocarcinoma which in 50 per cent of the cases, metastasizes to the heart muscle and is frequently seen in other rare locations. It is known that certain tumors such as the osteogenic sarcoma rarely grow within lymph nodes.

### Multiple Tumors

There is no doubt that in certain organs multiple tumors occur with greater frequency than on the basis of chance alone. The skin is very frequently the site of multiple carcinomas. This is particularly true in the male exposed to sunlight who develops the so-called tomato skin. Multiple carcinomas appear more quickly in this atrophic skin than it is possible at times to treat them. In this instance a large area of skin has been prepared for carcinoma.

In the oral cavity carcinomas may be multiple. If a patient develops one carcinoma of the oral cavity on the basis of leucoplakia and it becomes healed, then this patient's chance of developing another is fairly high. Sarasin studied slightly over 1000 cases of carcinoma of the oral cavity and found fifty instances in which more than one carcinoma had occurred. Gastrointestinal carcinoma is another type which often is multiple, as shown by the figures of Slaughter. These multiple tumors are particularly common in the large bowel. There is also an endocrine basis for multiplicity of tumors. In paired organs such as the breasts, testicles and ovaries if carcinoma appears in one organ the patient has a much higher chance of developing carcinoma in the opposite organ than a patient of the same age group who has had no cancer. In a recent paper by Warren in a series of 2829 cancer autopsies, 194 instances of multiple malignant neoplasms were encountered, an incidence of 6.8 per cent. The average interval between each successive tumor when it could be determined was 3.1 years. The greater frequency which was calculated as eleven fold must be attributed to some susceptibility or predisposition to cancer in some persons or groups of persons.

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## Chapter IV

### SURGERY OF CANCER

The surgery of cancer differs from surgery for nonmalignant lesions in that cancer surgery must *encircle the disease* and provide for its extirpation with a reasonable margin of normal tissue. Cancer surgery endeavors to stay away from the disease. This end is accomplished by an anatomic dissection which usually is planned completely before operation and is dictated by knowledge of the characteristics of the tumor and its type, location and mode of spread.

It cannot be denied that cancer surgery is specialized. Semken states the views of an advocate of specialization quite clearly when he says

"Incomplete operations by stimulating cancer growth tend to bring on conditions that are worse than the original process, and to result in increased suffering and earlier death. Secondary operations for recurrent cancer have seldom resulted in permanent cure. With these experiences as well understood as they have been for many years, it is surprising how many surgeons have failed to plan and carry out the logical cancer procedures in the important first operation, and even more that any surgeon would find satisfaction in the feeling that he 'got most of the cancer out.' Cancer surgery needs to be specialized—and specialization will mean not only that each cancer patient will have a better primary operation but also that many will be saved by operation whose condition would be considered inoperable by the average surgeon.

The field of cancer surgery is a most exacting one and the man who does a volume of this type of surgery and is able to live with and have others see his results must be a man with a rich background in broad surgical training.

Before surgery is undertaken, the presence, the location, the type, and extent of malignant lesions should be determined with as much exactness as possible. As a general rule, the conclusive evidence afforded by biopsy should be obtained before radical surgical procedures are started. When biopsy is impossible or unsatisfactory, the surgeon must resort to his clinical judgment and execute an attack on the disease that is decisive and effective. The time frequently comes at the operating table when the pathologist is powerless to help and when the background in pathology of the surgeon himself must be adequate to allow him to proceed with confidence into the proper channel of attack.

Once the diagnosis of cancer is established, the patient should be appraised from the standpoint of surgical risk and of whether the chances of complete recovery or relative benefit received justify the hazards of operation. In many instances, the operative risk in removing a malignant tumor is small enough to justify its accomplishment, but some cases require more careful appraisal. The

evaluation of risk varies with the type of surgery contemplated. But in spite of the immediate risk, an operation should be undertaken if it offers the patient a reasonable chance of complete recovery. Many of the patients requiring surgery are of advanced age, but it should be borne in mind that physical condition is a physiologic and not a chronological phenomenon. One patient of 70 years may be considered a remarkably good operative risk, whereas a patient of 60 may be found to have far exceeded the safe physiologic age for radical surgery.

The surgeon should be familiar with the evolution of all types of tumors. For instance, it has been shown that carcinomas of the rectum and rectosigmoid may exist for long periods of time and may even become partially fixed to surrounding organs, and yet from the standpoint of possible cure, a resection (taking portions of other organs) is justified. On the other hand, when a carcinoma of the stomach involves a major portion of the organ or has fixed it to other structures, surgery should be considered only palliative because the probability of the disease being beyond the operative field is high and the chances of cure are poor. The surgeon should know that when a cancer of the breast presents certain clinical findings surgery shortens rather than prolongs the life span even though a radical mastectomy is technically possible (Haagensen).

For noneancerous conditions, the concern of the surgeon usually lies in conserving structure and function and in leaving a satisfactory cosmetic result. The primary aim of the cancer surgeon is to execute an operation radical enough to wipe out the disease completely. As a general rule, if there is any doubt as to whether a structure is involved by cancer it should be resected without hesitation, for a conservative attitude almost invariably results in recurrence of the disease and death. For example, there is often a reluctance to do more than enucleate a soft tissue sarcoma on the argument that the patient is young, the tumor apparently does not have any serious effects, and frequently the family insists upon local rather than radical resection. As a result, very few soft tissue sarcomas are entirely removed and they quickly recur locally and metastasize distantly. Preservation of the facial nerve for an obviously malignant parotid tumor, simple mastectomy for a small early cancer of the breast, preservation of the anal sphincter rather than an abdominoperineal resection for a carcinoma of the rectum, lobectomy rather than pneumonectomy for a carcinoma of the lung, conservative rather than radical resection of skin cancers, local resection rather than amputation of malignant bone tumors are often carried out by surgeons unfamiliar with the pathology of the tumor with which they are dealing. If, after a thorough evaluation of a carcinoma, the lesion is considered worthy of a curative attack there should be no hesitation in completing the most radical procedure even if it involves sacrificing normal structures and impairing function. It is far better to have a permanent recovery with some impairment than to have an immediate good cosmetic result followed by an early death. On the other hand the radical approach of cancer surgery requires certainty in the diagnosis, for diagnostic errors may lead to unjustifiable mutilations.

**Contraindications to Surgery**—Only a very few cardiac lesions, particularly those impairing the circulation to the heart, mitigate against radical



surgery. A recent coronary thrombosis, aortic stenosis, aortic insufficiency, or irreversible advanced circulatory failure often obviate a major surgical procedure, for if hemorrhage and shock should occur, the falling blood pressure and loss of oxygen-carrying hemoglobin might result fatally in such cases. Hypertensive or arteriosclerotic well-compensated heart disease, however, should not be considered contraindication to major surgery. Congestive heart failure of a minor nature may be beneficially counteracted by proper medical treatment and often is not a serious contraindication for a necessary surgical procedure.

The renal reserve of patients submitted to radical surgery should be within reasonable limits. If the urine concentrates fairly well and there is only slight impairment of urea clearance with perhaps a slight elevation of the non-protein nitrogen, surgery need not be considered as particularly hazardous. If, however, evidence of major renal damage is demonstrated by an elevated nonprotein nitrogen (definitely not the result of prostatic obstruction, extrarenal azotemia or other factors), and if the urea clearance has fallen to dangerous limits, and other tests of kidney function are greatly impaired, then a major surgical procedure should not be undertaken because death from renal failure is too great a certainty to justify the risk.

**Preoperative Care** The preparation of patients for major cancer surgery is one of the very important phases of the surgical treatment. Unfortunately, most of the patients are over 50 years of age. Advanced ulcerating cancers are invariably accompanied by anemia, evidence of secondary infection, lowered serum proteins, avitaminosis, lowered prothrombin time, considerable weight loss, and poor general condition. Every effort should be directed to correcting these associated findings. Blood and serum protein levels can be raised by repeated transfusions or, better, by the use of hydrolyzed protein feedings or intravenous amino acid solutions (Amigen). The indications for using amino acids exist only when adequate oral protein cannot be given, because utilization is somewhat sacrificed by parenteral administration. It should not be forgotten that serum protein levels regarded as "low normal" can occur with almost complete exhaustion of protein reserve (Madden).

The necessity for both pre- and postoperative optimal nutrition has been little emphasized. Many of the patients, particularly those scheduled for abdominal surgery, have lost considerable weight, and consequently surgery is poorly tolerated for they show unstable blood pressure disproportionate to the degree of hemorrhage during operation (Varco). Varco has devised two diets, one to be taken orally and the other by tube. These diets are high in protein, high in carbohydrate, and low in fat. If necessary, 7,000 to 10,000 calories can be given daily over a period of time proportionate to the amount of weight lost. Varco feels that this diet lessens the operative risk inasmuch as restoration of nutritional balance is necessary in spite of an adjustment of water, electrolyte, and hemoglobin values.

If the lesion is abdominal and there is any evidence of intestinal obstruction, measures should be directed toward decompression with a Miller-Abbott or an intubating duodenal tube with continuous suction (Wangensteen), since the

procedure is well known to reduce greatly the operative and postoperative complications secondary to distention. The oral cavity may be made safer for surgery by the extraction of hopelessly carious teeth. Chemotherapy and antibiotics may play a most important prophylactic role in the preparation of the patient for surgery, following which infection is a likely complication. The administration of sulfonamides, which are used to inhibit growth of intestinal organisms, has become routine prior to surgery on the colon. Preparation of the patient until he is a reasonable operative risk may require prolonged strenuous and repeated measures, but in the majority of cases it can be done in ten days to two weeks.

**Anesthesia**—Because many radical operations for cancer are time consuming, the anesthetic must be one which can be given for several hours and yet give minimal postoperative complications. For abdominal cancer surgery, continuous spinal anesthesia has grown greatly in popularity (Lemmon, Cooper), since it allows excellent relaxation, has a minimum of risk, and can be supplemented with ephedrine to maintain the blood pressure, and with small intravenous doses of sodium pentothal if additional anesthesia is required. Continuous spinal anesthesia allows the surgeon to operate without hurry, and it allows the patient to be nursed through a prolonged trying procedure without being subjected to the additional hazard of an inhalation anesthetic.

General inhalation anesthesia for abdominal surgery is still selected by many surgeons. Ether and the various gases and their combinations have their various disciples. Intratracheal administration of general inhalation anesthesia has proved especially desirable for upper abdominal surgery. Curare with cyclopropane has gained much favor because of the excellent relaxation with light anesthesia and high degree of oxygenation.

The surgery for cancer involving the thorax and head and neck, like surgery for any other lesion in these regions is dependent on good anesthesia. A competent anesthetist is indispensable. The choice of anesthetic agent and means of administration should always aim to provide a high concentration of oxygen and an adequate airway. If the patient cannot be anesthetized and placed under perfect control, with good color and a free airway, it may be wise to cancel the operation. This is especially true if the operation is expected to be of long duration. The use of an intratracheal tube is very frequently the most satisfactory solution to both the adequacy of anesthesia and the adequacy of surgical exposure. The choice of anesthesia in a given case may be the major technical problem of the entire procedure and should therefore receive adequate thought and planning. Tracheotomy is frequently done following major surgery about the mouth and jaws. The performance of the tracheotomy early and the administration of the anesthetic through the tracheotomy tube is many times a happy solution to a difficult technical problem. Local anesthesia is quite adequate for many of the minor resections about the face and mouth and frequently in the form of regional nerve block, may be the choice for a major procedure. As a general rule the intravenous administration of sodium pentothal should not be used when the surgery involves the mouth and neck unless

there is absolute control of the airway by intratracheal tube or tracheotomy. Severe laryngospasm has resulted when pentothal has been used for these patients without adequate safeguard.

**Conduct of Operation**—The operative procedure is only one step in the treatment of a surgical cancer patient and shares importance with pre- and postoperative care. It deserves the same planning and attention to detail. Adequate assistance must be available. This means not only operating assistants and a nurse, but an adequate backlog of doctors and nurses who are experienced in the intricacies of the various procedures and who can always be called on when needed. The success of some involved procedures depends as much on operating room man power as it does on the skill of the surgeon. From the surgeon to the orderly, the operating room personnel should function as a team. Facilities for frozen section and expert interpretation are essential. Success in many cases will depend on the understanding and skill with which replacement therapy is conducted during the operative procedure. There is no suitable substitute for whole blood as a replacement agent, and its frequent use demands an availability of a blood bank. The extent of the operation, its duration, the amount of raw tissue exposed, and the bleeding involved should determine when and how much whole blood is necessary. Transfusion should be started early. To wait for elevation of pulse and drop in blood pressure before starting blood indicates an ignorance of the physiologic changes that are taking place during the operation.

An important technical trend is toward the use of alloy steel wire for closure of abdominal wounds as advocated by Jones. Closure by this technique has been a definite advance in cancer surgery for eliminating wound dehiscence and infection. It promotes healing of wounds without complications in spite of carcinomatosis, jaundice, or cachexia, and in addition it detracts from the dangers of wound disruption in early ambulation.

**Postoperative Care**—The postoperative care should be directed to restoring to the patient all normal physiologic functions. To do this, it is necessary to keep a careful record on all those functions which clinical and laboratory methods allow to be followed. Of vital importance are the treatment of anemia and hypoproteinemia. Water and electrolyte balance must be maintained. The nutritional state should be supported, and parenteral protein (amino acids), carbohydrate, and vitamins should be given as indicated. By carefully following the patient's biochemical status, it is possible to maintain balance until the critical postoperative period is past. With the re-establishment of peristalsis, the closure of fistulas, and the attainment of an adequate oral intake of the vital nutritional and chemical substances, the patient becomes self-sustaining. In order to carry a cancer patient to this stage, it is essential that the principles of parenteral feeding (Elman) and the maintenance of fluid and electrolyte balance (Collier) be clearly understood.

Early postoperative ambulation has been accepted with increasing enthusiasm as being of benefit to elderly cancer patients. It has definitely decreased the morbidity by reducing the incidence of postoperative complications.

and by preserving the physical well being of the patient. Unfortunately, it apparently does not cause a decrease in the incidence of deep leg vein thrombophlebitis (Blodgett).

Recent advances in the diagnosis and treatment of postoperative thromboses of the leg veins have placed this hitherto uncontrolled complication in the category of those amenable to active treatment. The subject is particularly important in the field of cancer surgery since so many patients fall into the age group in which phlebothrombosis and thrombophlebitis most frequently occur. It is beyond the scope of this presentation to go into the details of treatment of these conditions, many points of which are still controversial. Suffice it to say that early recognition and an energetic attack using venous ligation or anticoagulants as indicated will be an inseparable part of postoperative care of cancer patients if the incidence of pulmonary embolism is to be reduced (Homans, Allen, Hunter, Bruer, DeTakats).

**Reconstructive Surgery**—In the surgical treatment of cancer large areas of body surface and of the face and neck are often destroyed. There comes a time when such cases become reconstructive problems rather than cancer problems. Treatment should not be considered as complete until there has been a satisfactory cosmetic and functional restoration. It is not enough to cure an extensive carcinoma of the buccal mucosa by resection of the jaw and cheek, leaving the patient with an open, drooling mouth. All defects must be repaired or else the patient remains an unsightly or even hopeless cripple. The surgeon handling such lesions should have enough training in reconstructive plastic surgery to remedy any defects he makes or his original planning should provide for placing the patient in competent hands when the time for reconstruction arrives.

**Neurosurgical Procedures for Relief of Pain in Advanced Cancer**—A small proportion of the cases of advanced carcinoma present intractable pain. Spiller first introduced chordotomy to relieve pain below the diaphragm and later, Stookey performed high cervical chordotomy to alleviate pain from advanced carcinoma of the breast. White reported sectioning the spinothalamic tract to relieve pain in the upper neck and posterior scalp. However, these procedures are not without disadvantages. Incomplete sectioning of the spinothalamic tract results in failure. There is invariably a retention of urine which may be persistent. Intraspinal sectioning of the sensory roots (posterior rhizotomy) results in a complete loss of sensation in the areas supplied by these roots. The pain of advanced carcinomas of the maxilla, mandible and tongue should be cared for by measures directed to the ablation of sensation in various branches of the trigeminal nerve. At times intracranial sectioning of the sensory root is necessary. In most instances however, such palliative procedures can be avoided and satisfactory results obtained by intelligent progressive administration of analgesics and narcotics.

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The foregoing chapter can only be expected to touch on the broad general principles of cancer surgery and to emphasize some of its major aspects. Surgery is the only hope of cure in many malignant lesions, but the day is past when a

surgeon can be considered competent simply because he is technically capable of carrying an operation to completion. The cancer surgeon must be pathologist, amateur physicist, physiologist, and statistician as well as surgeon and philosopher.

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## Chapter V

### RADIOTHERAPY OF CANCER

Just over half a century ago, the searching observation of an austere German professor of physics resulted in the discovery of "a new kind of ray" which was later to be named, in his honor, the *Roentgen ray*. A few years later, a frail, young, and sentimental Polish woman Marie Sklodowska chose the subject of her thesis for a degree of Doctor of Sciences, and, without suspecting it, embarked on a most fascinating though trying voyage for an unknown destination. The discovery of a new element *polonium*, named after her country of birth was but a landmark in the search of this indefatigable woman, loving wife and tender mother as well as incomparable investigator. Inspired by the serene love and judgment of her French husband and collaborator, Pierre Curie, she pursued a long investigation which led them to the discovery of *radium*. And it was soon realized that the roentgen rays were artificially produced electromagnetic waves similar in nature and differing only in quality from the gamma rays of radium. These remarkable discoveries became but the preface of an interminable volume of interrelated discoveries of imponderable magnitude that were to change the old concept of immutable substances and indivisible atoms that were to project light in the history of matter and its evolution in the cosmos, and that were to lead man to irruption into the infinitesimal planetary system which is *the atom*, to grasp its secrets, and to acquire possession of the forces of his own destruction. The pleiad of scientists who wrote these new chapters forms a dissonant list of names: Planck, Einstein, Rutherford, de Broglie, Bohr, Irene Curie, Joliot, Lawrence, Compton, Chadwick, Fermi, Oppenheimer.

Radiotherapy, the application of ionizing radiations to the treatment of disease, remains the most constructive consequence of their discovery. The place that radiations hold in modern therapeutics is a credit to the few pioneers who persistently pursued the necessary research. The practice of radiotherapy requires a fundamental knowledge of electricity and of the physical properties of radiations, of radioactivity, of the production of roentgen rays, and of the interaction of radiations and matter. In addition, an intelligent application of radiations in therapeutics requires a knowledge of their effect on living cells and different tissues, in short, a knowledge of radiobiology.

Radiotherapy has been applied successfully to the treatment of skin diseases and its anti-inflammatory effects are put to great use in the treatment of a large number of affections of different systems. But the application of radiations to the treatment of malignant tumors is a considerably more serious undertaking in which their unique properties are exploited to a limit where irreparable damage may result and human life may be at stake. The empiric application of radiations (with forcefulness as well as with timidity) the unskilled balance of factors, their use where it is not properly indicated, often result in failures, accidents or at best in undeserved discredit. Improvements in

generating equipment and dosimetry have been welcomed, but rather than simplifying the practice of radiotherapy, they have redoubled the demand for skill. Even if no further improvements in equipment were to be made and our knowledge of physics were at an end, the results of radiotherapy of cancer could still be improved several fold by a more extensive understanding of radiophysiology, by a greater clinical control of the administration of radiations, and by an increased knowledge of the pathology of cancer among those who undertake to treat this disease. By knowledge of pathology is not here implied a mere pretense of microscopic recognition of cadaveric fragments of tumors but a thorough acquaintance with the life history of these malignant tumors (the rate of their growth, preferred modes of spread, radiophysiological response) that is a knowledge of their dynamic characteristics which is acquired by prolonged contact with cancer patients in the hospital wards and follow up clinics. What is learned at the autopsy table and through the microscope becomes then a meaningful complement.

The knowledge of physics, biology, and pathology and the necessarily wide clinical experience which is required of a competent radiotherapist imply a long versatile training. But only thus equipped can the radiotherapist succeed in the difficult and delicate task of applying his powerful means to the necessities of the case. Radiotherapy could hardly be called a superspecialty. It is indeed a rare example of the blending of varied disciplines to purposeful and significant ends.

### The Physical Foundation of Radiotherapy

In the gamut of electromagnetic waves which extends from the electric waves (100,000,000,000 cm. maximum wave length) through the radio waves to the visible light (0.0001 cm. maximum wave length) and ultraviolet rays, the roentgen rays, radium, and cosmic rays occupy the other extreme (to a known 0.000,000,000,001 cm. wave length). Radioactivity is the natural property of certain elements found in Nature and it consists of the spontaneous emission of radiations due to a disintegration of its unstable atoms. In therapeutics, radium is at present the most widely used of the radioactive elements but other elements or artificially radioactivated substances are also used. Roentgen rays are obtained by applying high potential electric currents to the electrodes of a specially designed vacuum tube. Other ionizing radiations such as neutrons, protons, and alpha particles have not yet been widely used for therapeutic purposes.

The beam of radiations which is produced in a roentgen ray tube is not homogeneous, the wave length of its constituents varying from a maximum to a minimum, an increase in the *kilovoltage* applied to the tube results in a lowering of the minimum wave length rays within the beam. Since their ability to penetrate matter is greater as their wave length decreases, an increase in kilovoltage results in a relative improvement of the penetrating ability of the beam of rays. The "superficial therapy" equipment used in dermatology is usually 100 kv or less, and the most common "deep therapy" equipment works at about 200 kilovolts. Roentgen ray equipments up to 1,000 kv ("supervoltage") have

been available in a limited number of places for several years. The development of the *betatron* by Kerst has opened the possibility of obtaining beams of roentgen rays of from 1,000 to 100 000 kilovolts. The designation of "mega-voltage" has been suggested for this new range (Leucutia).

As radiations hit matter they are absorbed in a variable proportion depending on their own quality and the nature of the matter. Metals absorb an increasing amount of radiations as their atomic number increases. The interposition of different thicknesses of metals (aluminum, copper, tin, lead) in the beam of roentgen rays results in the arrest of a greater proportion of 'soft' or longer wave length rays and consequently in a relative improvement of the quality of the beam. This is the principle applied and known as *filtration* but a filter is not exactly like a sieve (Quimby) since it adds its own imprint (characteristic rays) to the beam of radiations and it also arrests some of the 'hard' or shorter wave length radiations.

As the roentgen rays travel away from their source they disperse, at points increasingly distant from the target the beam is distributed over increasingly large surfaces which vary proportionately with the square of the distance. Consequently as the distance from the source increases the amount of radiations received by a given surface decreases with the square of the distance (inverse square law). In other words at distances of 10, 20, 30, 40, 50 cm., etc., from the target the amounts of radiations received by the same square surface vary as 1,  $\frac{1}{4}$ ,  $\frac{1}{9}$ ,  $\frac{1}{16}$ ,  $\frac{1}{25}$ , etc. Note that as the distance increases, there is less difference between the amounts of radiations received at two consecutive points. Thus the amounts received at points 10 and 20 cm. from the target differ from each other as 1 to  $\frac{1}{4}$  while the amounts received at points 40 and 50 cm. from the target differ only as  $\frac{1}{16}$  to  $\frac{1}{25}$ , or approximately as 1 to  $\frac{2}{3}$ . Consequently assuming the absorption and scattering to be zero the maximum amount of radiations which could be transmitted through an object 10 cm. thick placed 10 cm. from the target is  $\frac{1}{4}$  of the incident amount. But when the same object is placed 40 cm. from the target, the maximum possible transmission of radiations through its thickness rises to almost  $\frac{1}{4}$  of the incident amount. The *target object distance* is therefore of importance in the transmission of radiations in depth.

**Interaction of Radiations and Matter**—Among the various properties of radiations are their ability to produce fluorescence of certain substances (utilized in radioscopy), their photochemical effect (utilized in radiography) and their ability to discharge electrically charged bodies to produce ionization.

As radiations pass through matter there is an interaction of one on the other which results in a complex progressive transformation of the incident energy. Ionizing radiations are capable, by their high intrinsic energy, of disrupting the atoms of the matter they traverse. Because matter is made mostly of empty spaces it is perfectly possible for a ray or photon to pass through it without being affected but when it hits an atom the collision may have either of two types of effect. (1) the *photoelectric effect*, in which the ray loses its entire energy in the dislodgment of an electron from its orbit these dislodged electrons become negative ions each one of which may produce several thousand ion pairs along their zigzag path and (2) the *Compton effect*, in which the ray



loses only part of its energy in dislodging an electron (recoil electron) and proceeds, deviated from its original path (scattered photon), with a reduced energy but capable of further collision. The photoelectric collisions are most frequent in the interaction of low voltage radiations and matter, their number decreasing (but the range of the dislodged electron increases) as the voltage is raised. The Compton collisions become predominant (and the range of the recoil electrons becomes longer) as the voltage increases. The atom deprived of one of its electrons becomes a positive ion when another electron replaces the missing one, a *characteristic ray* is emitted, the wave length of which depends on the nature of the traversed element and the position of the dislodged electron.

The scattered or secondary radiations (photoelectrons, recoil electrons, scattered photons, and characteristic rays) which result from this interaction of radiations and matter may travel in the same direction as the incident radiations (forward scatter), but a portion of it takes a retrograde path (back scatter). Thus at any depth of matter, the amount of radiations received is the result of the addition of the unaltered part of the incident beam plus the forward scatter plus the back scatter. In radiotherapy of 200 kv, the unaltered part of the incident beam which reaches a point decreases rapidly with greater depth and becomes inferior to the amount of forward and even back scatter radiations. With supervoltage equipment of 1 000 kv or more, the unaltered part of the incident beam which reaches in depth remains the largest of the three components for a considerably greater depth, the forward scatter remains important but the back scatter is minimal.

**Measure of Quantity and Quality of Radiations**—The ability of roentgen rays to ionize gases has been utilized for measuring quantity, since the ionization produced is proportional to the quantity absorbed by the gas. An international unit, convenient because of its reproducibility, has been agreed upon: the *roentgen*. Ionization chambers or dosimeters which report the amounts of radiations in roentgens are currently used. Because the range of dislodged electrons varies with the change in voltages, the dimensions of the ionization chambers must be changed accordingly or the chamber differently constructed for radiations of different quality, thus, an ordinary dosimeter cannot be used to measure the radiations emanating from radium, for instance, in order to express them in roentgens.

For a long time, the quantity of radiations delivered by radioactive sources has been expressed in *millicuries destroyed* and also by the product of the amount of radium used and the time of exposure, that is, in *milligram hours*. Both of these expressions have the disadvantage of being doses at the source and not doses absorbed. Under specified circumstances, *milligram hours* can be expressed in gamma roentgens.

The qualitative composition of a beam of rays, the relative proportion of radiations of shorter or longer wave length, is obviously of importance in the appreciation of physical possibilities. To obtain this information, a long spectroscopic analysis or other complicated studies are necessary. For practical purposes, the quality of a beam may be appreciated by a study of the absorption curve when it passes through increasing thicknesses of a given material. Since

what is generally required is a general idea of the penetrating ability of the beam, it has been agreed that this is simply expressed in a single figure by the *half value layer*, this is an expression of the thickness of material which reduces the incident dose in half and is usually expressed in millimeter thicknesses of aluminum or copper. It must be remembered, however, that while working with beams emanating from different sources, one may reach an expression of the same half value layer with beams of very different qualitative compositions.

### Biologic Effects of Ionizing Radiations

The administration of an excessive amount of radiations to any living tissue results in damage to its different components, a damage which is greater nearer the source of the radiations but affects indiscriminately all living cells in the field in what has been termed a *diffuse cytocaustic effect*. This effect differs in no way from that which is due to an excessive application of heat, cold or caustic substances (Regaud). On the contrary, appropriate amounts of radiations of good quality may traverse the superficial layers of tissues without affecting them and only have an effect upon certain more deeply situated cells, this latter phenomenon, the *selective cytolethal effect*, is the one utilized in radiotherapy of malignant tumors.

The lethal effect of radiations on living cells is the final result of the ionization produced in their collisions with the components of living tissues. But while the death of the cell may immediately follow in some instances, the damage done may become ostensible only after the cell undergoes mitosis and still in other instances it is only appreciable in the cell's descendants. Bergonie (1904) noted no visible changes in the appearance and movements of spermatozoa irradiated in vitro, but Bardeen and Regaud (1908) demonstrated that irradiated spermatozoa were either rendered unsuitable for fecundation or resulted in abortive or monstrous fecundations. Guilleminot irradiated dry grain and found that it kept a latent lesion which brought about anomalies and death at some stage after its germination; the same was true of grain which was not planted for several months following irradiation.

The expression *lethal dose* has no significance in radiobiology. Cells of the same species simultaneously irradiated die after receiving extremely variable amounts of radiations. The introduction in biology (Crowther, Condon) of the idea of the discontinuous absorption of the incident energy furnished Lacassagne and Holweck with a means of conceiving the action of radiations on the cell. Working with different unicellular organisms they found that irradiation induced several types of lesions among the individuals treated and that the relative proportion of these lesions varied with the dose. Interpreting these facts according to the quantum theory (corpuscular nature of radiations), Lacassagne (1934) and Holweck attributed these lesions to different qualitative and quantitative action of radiations on the individual cells.

1 *Immediate death* due to simultaneous absorption of a large number of particles in the cell, resulting in destruction of the different cellular constituents

biopsy is possible. If the tumor is voluminous and nonnucleated, aspiration biopsy will obtain adequate material to substantiate the diagnosis. We feel that aspiration biopsy in the diagnosis of questionable tumor of the breast is not indicated as a basis for therapeutic decisions (see chapter on pathology). The material obtained may be difficult to interpret, and a diagnosis of a benign tumor may be obtained in the presence of cancer. This may give a false sense of security. Biopsy through the nipple may be done but is not always practical (Leboigne). On surgical exploration of the breast, an experienced surgeon is able to recognize the nature of the lesion in over three-fourths of the cases. However, if frozen section is necessary for the diagnosis, the attitude of the pathologist should be conservative. If the lesion is definitely malignant, then radical mastectomy should be done, but if it is definitely benign, local excision followed by careful histologic examination should be carried out. If there is any question in the diagnosis, a biopsy should be taken, the surgical incision closed, and the patient returned to the ward until multiple sections of the material can be studied. If the lesion proves to be malignant, no harm has been done by having the patient wait forty-eight hours for operation.

*Examination of the Pleural Fluid*—At times the tumor may have spread to the pleura from which bloody pleural fluid can be obtained. This can be centrifuged and sectioned, and at times, a diagnosis obtained from it.

*Biopsy of Metastases*—Sometimes there is supraclavicular lymph node involvement which may be biopsied in cases in which there is only questionable operability. In a few instances, skin nodules may provide a means of diagnosis of either the primary tumor or of a postoperative recurrence.

**Differential Diagnosis**—*Chronic cystic mastitis* is a benign lesion often confused with carcinoma of the breast. Chronic cystic mastitis is a misnomer, fibroadenomatosis with or without cyst formation is probably a better term. It usually occurs in parous women with small breasts. The condition may disappear during pregnancy. Local recurrences or the development of new lesions in the opposite breast are common. It is present most commonly in the upper outer quadrant but may occur in other quadrants and eventually involve the entire breast. It is often painful, particularly in the premenstrual period, and accompanying menstrual disturbances are common. Nipple discharge, usually serous, occurs in approximately 15 per cent of the cases, but there are no changes in the nipple itself. The lesion is diffuse without sharp demarcation and without fixation to the overlying skin. Multiple cysts are firm, round, and fluctuant and may transilluminate if they have clear fluid. A large cyst in an area of chronic cystic mastitis feels like a tumor but it is usually smoother and well delimited. The axillary lymph nodes are usually not enlarged.

Gross examination of chronic cystic mastitis rather infrequently shows large bluish cysts (blue dome cysts of Bloodgood). More often, however, the cysts are multiple and small, with intervening increased yellowish gray parenchyma. The cysts contain serous or viscid liquid. The yellowish gray tissue cuts smoothly and does not show the chalky streaks of carcinoma. The process is very frequently bilateral (Reclus).

clinical impressions can be. A series of cases was analyzed at our hospital and the following figures were obtained:

EVALUATION OF AXILLARY LYMPH NODES	CASES
Negative, agreed upon clinically and pathologically	29
Positive, agreed upon clinically and pathologically	29
Negative clinically, positive pathologically	7
Positive clinically, negative pathologically	11
	<hr/> 101

Certain general conclusions can be drawn from this. In the first place, if a large hard node (greater than 3 cm.) or one that is fixed is found in the axilla it is usually carcinomatous. The most common error is the clinical inability to detect some nodes which are already invaded. Inasmuch as the axilla is a large space, nodes may be missed and positive nodes may be very small and easily lost within the axillary fat. When there is ulceration of the primary tumor, the nodes are often enlarged and firm due to inflammation, and the usual clinical error is to consider these nodes metastatic.

*Transillumination* of the breast may give additional information for the differential diagnosis of breast lesions (Cutler). This should be done in a totally dark room with an intense light so that good visualization of any mass within the breast is possible. It is of particular value for the recognition of cysts and hematomas and for the localization of duct papillomas. Cysts containing clear fluid are translucent, but if the fluid is milky or bloody, then they may be opaque. Hematomas do not transilluminate. Transillumination is of no value in differentiating between a benign solid tumor and a malignant tumor (Cutler).

The clinical examination of a male patient with carcinoma of the breast does not differ from that of carcinoma of the female breast. The tumor, however, is more frequently seen within the region of the nipple, often has a longer history, and frequently shows ulceration. This occurred in 38 per cent of the 418 patients reported on by Wainright. It is the most frequent tumor affecting the male breast.

*Röntgenologic Examination*—If radical mastectomy is contemplated for a carcinoma of the breast and there are no symptoms suggesting metastases, a roentgenogram of the chest is indicated to rule out pulmonary involvement. If there are symptoms suggesting bone metastasis, then other roentgenograms should be taken as indicated. In some institutions routine skeletal films are done including chest, skull, dorsal and lumbar vertebrae, and pelvis, all of which are the most frequent sites of bone involvement. Fractures, intense pain, or symptoms suggesting sacroiliac disease may be signs of metastatic disease. Roentgenograms show a destructive process of the involved bone or bones for these lesions are usually bone destroying rather than bone producing. There may be multiple lesions but with symptoms referable to only a few of them.

The roentgenologic examination of the breast with or without injection of opaque material through the nipple has also been used in the diagnosis (Lockwood, Leborgne).

*Methods of Obtaining a Positive Diagnosis*—In all patients who are operated on a pathologic diagnosis is assured. In all other patients a biopsy should be done as a matter of record. If the lesion is ulcerated, an incisional

or intraacinar. The intraacinar variety, because of the rapid growth of connective tissue, has a predisposition to the formation of intraacinar invaginations.



Fig. 666—Gross specimen of fibroadenoma (weight 1500 Gm) in a girl 20 years of age.

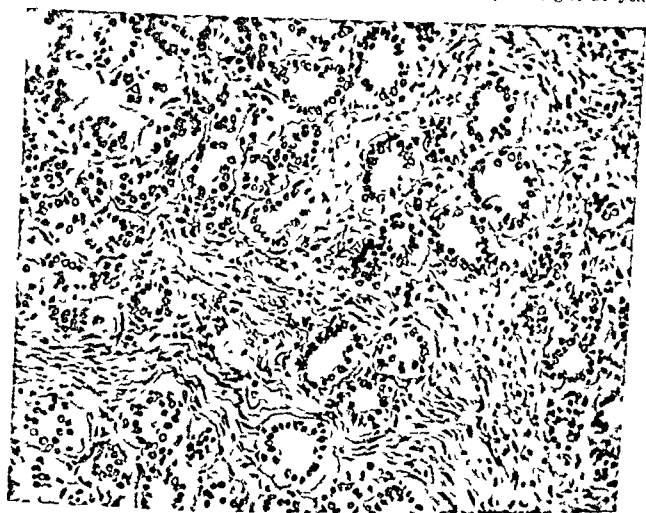


Fig. 667—Photomicrograph of fetal type of fibroadenoma (low power)

Although the fibroadenoma is not a precancerous lesion, it is a discrete tumor in which the stroma on rare occasions over a long period of time may be the site of origin for a fibrosarcoma. In some instances it is clinically impossible to be certain that the lesion is a fibroadenoma, and it is always simpler to excise

Sclerosing adenosis only rarely forms a palpable tumor. It is very frequently focal and may be mistaken for carcinoma both grossly and microscopically. At the Memorial Hospital about twelve cases were found in 1,000 operations for tumors of the breast in one year (Loote and Stewart). The following description of the gross findings is summarized from the excellent description by Loote and Stewart. Sclerosing adenosis most often occurs in patients 20 to 30 years of age. The growth is freely movable in the breast; its consistency is less rubbery than that of a fibroadenoma and instead of a smooth globoid shape the tumor may exhibit some nodularity and varying coarseness.

If the clinical impression of carcinoma is carried to a surgical exploration with frozen section there is danger that the microscopic examination will add further confusion. On section it shows indefinite encapsulation and a grayish white or pinkish yellow surface but the chalky streaks so commonly observed in carcinoma are usually absent. Most important is the usually definite lobulation. Many changes can be observed in the ducts and connective tissue stroma. Some of these are significant but others may be due to advancing age and nonspecific inflammatory processes. The proliferative changes are most important. When one change is present others are also usually observed. These include apocrine epithelium, blunt duct adenosis, papillomatosis and sclerosing adenosis. There is proliferation of the stroma and the connective tissue may increase and distort the architectural pattern so that a false impression of proliferation and invasion is given. However, mitoses are absent and the nuclei are very regular in appearance. This process is due to an excessive multiplication of both extra- and intra-lobular portions of the mammary parenchyma (Loote and Stewart). Certainly all patients with sclerosing adenosis discovered before the menopause should be followed indefinitely at six month intervals.

According to Stout simple mastectomy is indicated in the cases of fibroadenomatosis in patients with a familial history of cancer and in patients in whom there are clinically suspicious nodules of extreme hyperplasia.

*Fibroadenomas* are common lesions of the breast. That some relationship exists between these tumors and hyperestrogenism is supported by the fact that they can be produced with estrogen in animals. Fibroadenomas occur at a much earlier age than does cancer, is the most common between 20 and 35 years of age (peak age incidence from 21 to 25 years). Fibroadenomas are usually painless but may be tender; the nipple itself is usually normal; there is no discharge and there are no skin changes unless the tumor has reached a large size; they are freely movable and firm with smoothly lobulated boundaries in contrast to the indefinite outlines of carcinoma. These tumors often grow rapidly at the time of pregnancy or lactation. Multiple tumors occur in about 15 per cent of the cases. New fibroadenomas frequently appear in the breast which has contained the disease but may occur in either breast.

On gross examination fibroadenomas exhibit a well defined capsule with a slightly nodular surface (Fig. 666). The cut section shows them to be lobulated, yellowish gray and homogeneous in character. There are none of the chalky streaks so characteristic of carcinoma. At times they are associated with cystic disease of the breast. Microscopically they are classified as pericanalicular

it locally. At the time of operation, its characteristic appearance is easily recognized. If there is any doubt as to the gross diagnosis, frozen section can determine its character in 90 per cent of the cases.

*Benign intraductal papillomas* occur in women between the ages of 20 and 65 years. Both the benign intraductal papillomas and malignant papillary adenocarcinomas occur most frequently in the region of the nipple and areola. Very often the two appear in conjunction with each other. The benign papilloma is often soft and cystic and located in the central portion of the breast beneath the nipple, which is usually normal. A sporadic discharge occurs in nearly 50 per cent of the cases and this is more frequently bloody than serous. Pain is evidenced if and when sudden hemorrhage into a dilated obstructed duct takes place. At the time of obstruction, the tumor may enlarge, but if nipple discharge follows, the tumor may diminish to such a degree that it can no longer be felt. This reduction may completely relieve the pain. The mass is usually movable unless infection has caused fixation and retraction of the nipple. The axillary lymph nodes are also firm and enlarged if infection is present.

On section of the tumor, a cauliflower growth or villamentous tumor is seen protruding into a cyst (Fig 668). The cyst may contain a brownish-yellow fluid and evidence of old hemorrhage. The papillary growth within the cyst is often multiple and may vary in size from 1 to 10 cm in diameter. Occasionally an intraductal papilloma occupying one duct may show evidence of carcinomatous change in only one portion, and because of this coexistence it has been suggested that the malignant tumor develops from the benign one. Hart, however, believes that an adenocarcinoma is malignant from the start. Saphir studied fifty-eight cases of benign papillomas and divided them into three distinct types according to their origin: the first type arising from connective tissue outside the duct (forty-two cases), the second type arising from glandular tissue outside the duct (nine cases) (both of these types gradually invaginated into the duct), the third type (seven cases) arising from duct epithelium and behaving very much like the transitional-cell carcinomas of the bladder and pelvis of the kidney. This third type had a tendency to extend locally and implant along the ramifications of the duct system.

There are three possibilities of confusing a benign papilloma with carcinoma. (1) If infection develops in the papilloma, it causes fixation to the skin and retraction of the nipple, (2) sections taken through the walls of a cyst may show remnants of acini or ducts, which are sometimes mistaken for carcinoma, (3) on sections taken at peculiar angles or cut tangentially, an incorrect diagnosis of papillary adenocarcinoma may be made. As Cheatele emphasizes, multiple sections should be taken in order to study carefully the distribution, number, and character of the papillomas within the breast. If on microscopic examination of a biopsy, the tumor should be either of the first two types outlined by Saphir, a circumscribed region of breast tissue should be removed with the tumor because of its tendency to be multiple. If the third type is discovered, then a radical mastectomy should be performed. When the intraductal papilloma is located away from the nipple, it has a tendency to be more malignant (Stout, 1946). If it recurs after a simple excision, the entire breast should then be

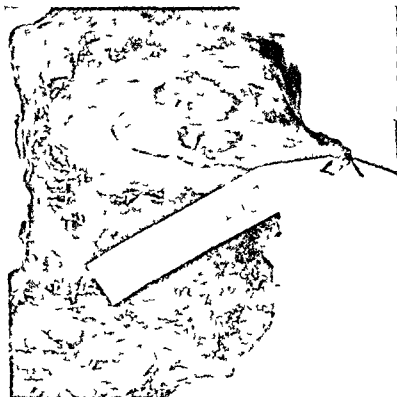


Fig. 668.—Intraductal papilloma with papillary characteristics and delineation near the base of the nipple. (Courtesy of Dr. Arthur Lurdy Stout, Department of Surgical Pathology, Columbia University, New York, N. Y.)

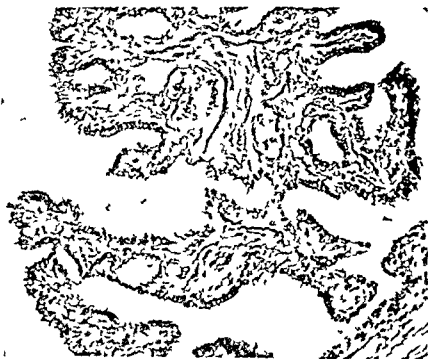


Fig. 669.—Photomicrograph of an intraductal papilloma. (low power)



on physical examination. Biopsy alone gives the diagnosis, although the history of the case does give important clues as to the nature of the lesion.

Some of the less common specific types of carcinoma may cause difficulty in differential diagnosis. *Paget's disease*, because of its long duration, is often confused with inflammatory lesions of the nipple, some of which begin on the areola, a finding which may in itself rule out Paget's disease. Inflammatory lesions often quickly clear under symptomatic treatment. Eczematoid lesions appear in young girls, but Paget's is a disease of older women and is seldom seen in patients under 25 years. Intraductal papillomas associated with infection and inflammation may be confused with Paget's, but these tumors usually have a bloody discharge and may also be differentiated by palpation. Biopsy may be necessary, however, to prove the diagnosis conclusively.

*Comedo carcinomas*, because of their size and the absence of axillary node involvement, may be confused with cystosarcoma phyllodes, which are usually cystic and are even more infrequent than the comedo carcinoma. Biopsy of course easily decides the diagnosis, which should be made before operation inasmuch as the treatment for these two diseases differs. As about 40 per cent of the comedo carcinomas are centrally located, they can also be confused with large intraductal papillary cystadenomas or papillary adenocarcinomas. In both of these conditions the tumor is located in the region of the nipple and discharge is evident. The papillary cystadenomas increase and decrease in size because of variations in obstruction in the main ducts. They are usually cystic, however, and rarely reach the size of the comedo carcinoma.

*Inflammatory carcinoma* is very commonly confused with erysipelas. Grossly, the distinguishing features of these two diseases are much the same. However, in erysipelas the constitutional symptoms are much more severe, and the fever and leucocytosis much higher. Erysipelas rapidly regresses under the sulfonamides. It may occur during pregnancy or lactation and, in turn, be confused with mastitis. But if the supposed mastitis lasts more than two weeks, biopsy is indicated.

### Treatment

**Surgery**—Radical mastectomy is the only treatment that offers any certainty of cure for carcinoma of the breast. This must include removal of the entire breast, overlying skin and entire pectoralis minor, the sternal portion of the pectoralis major, the deep fascia extending down to the recti muscles, and the axillary contents. Lymph nodes may all be on the anterior surface of the pectoralis major muscle (Wainwright). The deep fascia of the recti muscles must be removed because lymphatic vessels are present in this fascia (Handley). Since clinical appraisal of a metastasis to the axillary nodes is notoriously inaccurate, there is no justification for doing anything less than the radical procedure if the case warrants operation at all. Any compromise procedure is not justified. Because of advances in both the selection of cases and surgical technique, the operative mortality is now 1 per cent or less. It must be stressed and recognized, however, that in many instances of advanced carcinoma, surgery is not indicated and may even hasten the death of the patient.

removed. *Granular cell myoblastoma* can simulate breast carcinoma exactly both clinically and grossly. Its true nature will be revealed only by frozen section (Haagensen).

*Fat necrosis* is relatively infrequent in the breast. It arises following trauma and its clinical characteristics mimic with great exactitude those of carcinoma. Occasionally fat necrosis occurs on the scar of a mastectomy and it is prone to occur in large, fatty pendulous breasts. It may be attached to the skin, feel very superficial, have indefinite margins, be almost stone hard and is usually accompanied by severe pain. On gross examination these lesions resemble carcinoma except for their somewhat greasy surface. Frozen section will reveal their true nature. Microscopically these cases always show duct stasis with periductal inflammation. If trauma occurred to a breast showing these pathologic alterations the development of fat necrosis would seem logical (Foot and Stewart). Simple excision is sufficient treatment.

*Plasma cell mastitis* must be very rare indeed. Stout and Warren have never seen a case of it and we have seen no example of it in our hospital. In 100 cases reported by Adair the average age was 36 years. It almost invariably occurs in married women, the first symptoms consisting of pain accompanied by a localized redness and sometimes a discharge from the nipple. Many of its clinical manifestations are similar to those of cancer, such as retraction of the nipple, skin adherence, edema, and enlarged axillary lymph nodes. Because of these alterations radical mastectomy is often performed without previous biopsy.

Grossly the changes may involve large areas of breast parenchyma. Usually there are a few small foci where softening due to inflammation is present. Microscopically there is evidence of a subacute inflammation of the duct system and sheets of plasma cells are extremely abundant. Bacteria are infrequently present.

In one case which we suspected of being plasma cell mastitis three large biopsies were taken all showing inflammation of the ducts plus widespread plasma cell infiltration. The gross examination of the specimen, however, showed a small carcinoma located 5 cm. from the overlying skin.

An incisional biopsy of deep masses in the breast or axillary nodes may be of value in differentiation from carcinoma. However if there is any doubt as to the nature of the lesion, and in particular because plasma cell mastitis may mask underlying carcinoma, exploration with frozen section should be done on any case in which the slightest suspicion of cancer exists.

*Tuberculosis* of the breast is very rare. It occurs at an earlier age than cancer usually between 20 and 40 years and is probably a secondary manifestation of pulmonary tuberculosis. As a rule the infection is hematogenous in origin but occasionally it represents a direct extension from a tuberculous empyema. The lesion is nearly always unilateral, presenting multiple irregular slowly growing nodules. Some of these coalesce and rupture with persistent sinus formation. In rare cases the tumor may be very hard because of the overproduction of connective tissue may have indefinite margins, and may be attached to the skin. It is impossible to differentiate these cases from cancer.

pause. Improvement occurred in about 15 per cent and there were no differences in results whether they were castrated by radiations or surgery.

In certain instances of carcinoma of the breast with osseous metastases, Ritvo has shown that sterilization by radiations may be of considerable value. Recalcification of osteolytic bone lesions may take place together with marked relief from pain and prolongation of active life. It is impossible to say whether life

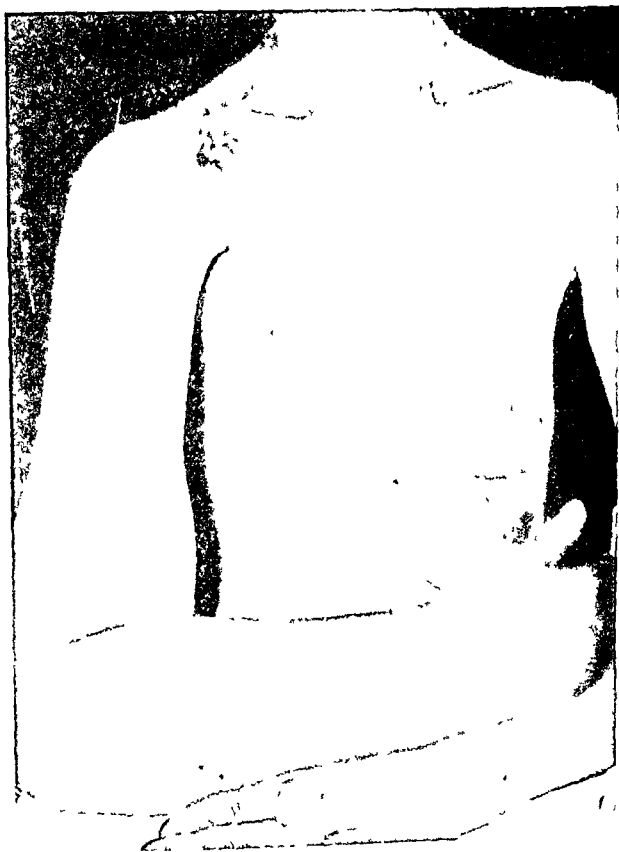


Fig. 670—Marked postoperative edema of the arm and recurrence in the infraclavicular region

is prolonged by castration. Ritvo did not recommend routine roentgen sterilization in premenopausal patients who did not have evidence of osseous metastases, but he felt that about one-third of the patients with bone metastases did receive relief. New metastases occur after castration, and this form of treatment apparently has no effect upon visceral lesions.

There is no evidence that when there is no sign of bone metastases, routine sterilization after radical mastectomy results in any favorable effect (Ahlborn).

*Contraindications to Surgery*—The absolute physical contraindications to operation which Haagensen and Stout have outlined include

- 1 The inflammatory type of carcinoma of the breast
- 2 Cases with extensive edema of the breast when the edema involves more than a third of the skin area
- 3 Satellite tumor nodules in the skin over the breast
- 4 Edema of the arm
- 5 Intercostal or parasternal nodules
- 6 Suprclavicular metastases
- 7 Distant metastases
- 8 Breast tumors developing during pregnancy or lactation

Haagensen and Stout believe that if surgery is performed when these symptoms are present, the duration of life after operation will be shorter than if no treatment is instituted. Certainly skin recurrences will be frequent and distant metastases almost inevitable. Moreover the operative mortality is high when the above conditions exist. If roentgenographic examination shows a single questionable metastasis to the lungs and from every other standpoint the case is operable surgery should be done because these apparently metastatic lesions may be due to nonspecific inflammation or healed tuberculous foci. The same applies to questionable bone lesions.

*Physical Symptoms Not Necessarily Contraindicating Surgery*—(1) A hard node in the suprclavicular region should be proved metastatic by aspiration or formal biopsy. In three of our patients nodes in this area proved to be tuberculous, (2) ulceration of the skin is not in itself a contraindication for it may occur in tumors of long duration and large size which still have not metastasized. (3) solid fixation of the tumor to the chest wall is not an absolute contraindication for frequently inflammation surrounding the tumor spreads to the pectoral fascia but true invasion of the pectoral muscles has not occurred. (4) a node larger than 2.5 cm. in transversal diameter does not militate against operation. We have had several cases in which a single node measuring up to 4 cm. was involved by tumor, yet the subsequent course was very satisfactory.

The treatment of the cystosarcoma is usually a simple mastectomy with removal of the pectoral fascia. If there is any doubt as to the extent of tumor invasion in the pectoral muscle then both the pectoralis major and minor should be removed and the axilla dissected. Emphasis is placed on removing the pectoral muscles because these tumors tend to recur locally. If simple mastectomy without removal of the pectoral muscles is followed by recurrence the prognosis is poor but not necessarily hopeless and a wide removal of the recurrence pectoral muscles and axilla is then indicated.

*Castilation*—Loeb first insisted upon the importance of ovarian factors in carcinoma of the breast in mice. Wintz was one of the first to advise the method of ovarian sterilization of all patients with carcinoma of the breast. Adair reported on 33 patients with mammary carcinoma castrated either by radiation or surgery. Every patient with involvement of the axilla local recurrence or distant metastases was so treated except those beyond the men-

2 *Delayed growth* resulting from partial disintegration of the protoplasm

3 *Suppression of motility* resulting from an impact on the motor centers

4 *Suppression of reproduction* resulting from destruction of the centriole

5 *Abortive anomalies of cellular division* due to the destruction of varying quantities of nuclear chromatin

6 *Hereditary malformations* due to a lesion of a particular segment of chromosomic substance (gene)

*"It is this dissociation of the cellular functions, this veritable microdissection, that characterizes the biologic effect of ionizing radiations in contradistinction with all other physical and chemical agents"* (Lacassagne, 1934)

The effects of radiations on living cells cannot be explained, however, on the basis of physical trauma alone nor can the complicated organization of normal tissues be considered, for the understanding of radiobiology, as the equivalent of an aggregate of unicellular organisms. The chemical effects of ionization of cellular components the possible changes of the permeability of the cellular membrane the ionization of circulating minerals and their effect on the interchange of fluids (Iailla Reynolds), and the effects of irradiation on the connective tissue on the blood supply, etc. contribute, in all probability, in a lesser or greater extent to the final results.

Living tissues react very differently to irradiations. Tissues formed by uniform cells not usually arranged in layers (nervous system, muscle, bone) generally show very poor radiosensitivity (Boiak), their injuries through irradiation are usually an indirect consequence due to resulting fibrosis or impaired vascularity. Tissues composed of multiform cells in continuous transformation, usually arranged in several layers (epidermis, seminiferous tubules), present marked radiosensitivity. But the individual cells of these complex tissues show a very variable degree of response to irradiations the germ cells (spermatogonias, basal cells of epidermis, lymphoblasts) being considerably more affected than their somatic descendants, this results in an apparent latency of the effects which may not make themselves evident for several weeks. Perthes first noticed the correlation of reproductivity and radiosensitivity of cells, Regaud and Blane established the basic experimental facts which were confirmed and expressed in the form of a general radiobiologic "law" by Bergonié and Tribondeau.

The effect of radiations on living cells is the more intense (1) the greater their reproductive activity, (2) the longer their mitotic phase lasts and (3) the less their morphology and function are differentiated.

In its general application, this "law" has often been found inaccurate its relative value is confined to the explanation of the different radiosensitivity of cells within the same tissue, which may be due to the greater vulnerability

We feel, however, that in young women with bone metastases there is nothing to be lost by sterilizing the ovaries preferably by radiations

Castration in carcinoma of the male breast has produced very striking clinical results with dramatic alleviation of bone pain regression at times of pulmonary metastases, and definite regression of the primary tumor The number of patients treated in this fashion has, however been small (Adair and Treves) Leventhal reported two cases with striking improvement of osseous metastases but there was little effect on local recurrences and visceral metastases

Testosterone propionate has recently been used for palliation in advanced carcinoma of the breast In four of eleven patients treated by Adair, there was regression of the metastases in both the soft parts and in bone Nathanson has treated advanced cancer of the breast with relatively large doses of stilbestrol In certain instances particularly in older women there was a favorable but temporary regression of the primary neoplasm Evaluation of this type of treatment is premature because of the small number of patients treated and the short follow up

**RADIOTHERAPY**—Except for epidermoid carcinomas the treatment of carcinomas of the breast is never primarily a radiotherapeutic problem if the disease falls within the realm of operability The palliative effect of local irradiations on inoperable carcinomas of the breast was recognized early (Gocht), as applied to the reduction of pain to the healing of superficial ulcerations or to the avoidance of such ulcerations radiotherapy has a definite place Not infrequently large ulcerations may be entirely healed (Figs 671 and 672) but it is unlikely that this results in a prolongation of life unless it is through the avoidance of complications Radiotherapy may be applied with equal benefit to recurrences on the scar of a mastectomy Sometimes there is only a negligible response and a questionable benefit from irradiation The histologic character of the tumor is seldom consistent with its response to irradiations (Stewart) Lenz reported that in contrast with what might have been expected a large proportion of undifferentiated tumors showed a lack of response to irradiations In spite of the possible failures, a thorough irradiation of inoperable lesions may contribute a few satisfactory results (Figs 673 and 674) By using the rigid criteria for operability of Hargensen and Stout a number of patients with locally advanced disease but without evidence of distant metastases are judged inoperable An attempt to treat these patients solely by roentgentherapy is then justified Lenz (1946) reported a thoroughly studied group of inoperable cases in which the patients were treated by roentgentherapy Of thirty one patients who received an adequate dosage ten lived without evidence of recurrent or metastatic disease for five years or longer These results are the product of individual attention and painstaking effort These treatments should be protracted over several weeks with the beam of roentgen rays directed tangentially in order to avoid as much as possible the irradiation of the lung Irradiation of the axillary and supraclavicular metastases may also diminish pain and edema of the arm but in general the benefit obtained in such cases seems hardly worth the effort

Radiotherapy finds its most useful indication in the treatment of bone metastases from carcinomas of the breast Early roentgentherapy to metastatic

lesions of the vertebrae rapidly eliminates pain and avoids collapse of the vertebrae and subsequent paraplegia. Elsewhere, radiotherapy to a metastatic lesion of the bone may circumvent a fracture or help to recalcify one that has already occurred. The recalcification of these lesions occurs with a variable intensity in different individuals. Radiotherapy has an unquestionable anodyne effect in the treatment of osseous metastases, which, in itself, is sufficient reason for its indication (Lenz 1931). Unfortunately, when bone metastases are present the disease is already generalized and a long survival cannot be expected.



Fig 671

Fig 672

Fig 671—Advanced ulcerative carcinoma of the left breast with voluminous axillary metastases.

Fig 672—Same lesion showing healing and clinical disappearance of the axillary adenopathy following intensive radiotherapy. Patient later developed supraclavicular and distant metastases.

Despite the careful selection of cases and high surgical skill, about a third of the failures in the treatment of carcinoma of the breast with axillary metastasis are due to regional recurrences (Haagensen, 1942). Because of this, the support of radiations has been sought as a *postoperative* measure following radical mastectomy. The purpose is to destroy any tumor cells which might be left and thus avoid these recurrences. Pusey applied this principle of "prophylactic" roentgentherapy following radical mastectomy in the very early days after the discovery of the roentgen rays. This conduct has been further expanded and ardently defended by outstanding surgeons and radiotherapists (Beclère, Larsen, Wassink). It has been the subject of lively controversy for over three decades. Portmann has presented convincing statistics in favor of systematic postoperative irradiation, basing his conclusions on a greater percentage of five-year survivals and a relative prolongation of life. Adam (1940) is equally vehement in advocating this complementary step of the surgical pro-

CANCER OF LARYNX (C.L.D.)

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cedure when the axillary nodes are found involved. He feels that the outstanding results which he has obtained do not require any further comparison with controls. Actually the life expectancy of failures and the percentage of five-year survivals depend greatly on the widely different concepts of operability and operative skills. Such concepts and skills change in time at the different institutions so that the results of treatment are not comparable. Radiotherapy, on the other hand, cannot be expected to have any influence upon the failures which are due to distant metastases without regional recurrences. It is consequently desirable that statistics on this subject be presented on the basis of the proportions of local recurrences in the postoperative irradiation and control groups. Haagensen and Stout found that the percentage of local recurrences was greater in the group receiving postoperative irradiation than in that without it, although the five-year survival was slightly better for the irradiated group, their criteria of operability were applied in these cases. It is interesting to note that Perthes (1920) strongly rejected the practice of postoperative roentgentherapy as dangerous on a similar observation, the greater proportion of recurrences in the irradiated group is obviously coincidental.

On a purely radiophysiologic basis and in spite of statistics, doubt may be expressed as to the value of systematic postoperative irradiation as it is practiced today. There is no proof that disseminated tumor cells, no matter how few in number, are more radiosensitive or radiocurable than the tumors from which they originate (Beclere, 1924). The dose required for the permanent sterilization of these tumors is far above that which is commonly administered as a postoperative measure (Harris, Lenz, 1946).

There are some instances in which at operation, particularly upon dissection of the axilla, the surgeon realizes that the tumor has been cut through or that it extended beyond the limits of resectability, or following operation the thorough pathologic study of the surgical specimen reveals this same ominous finding. In such cases, a thorough postoperative irradiation of the axilla is indicated as an additional recourse. But then the radiations must be administered in sufficient dosage if a permanent effect upon the remaining tumor is to be expected. The results of the procedure are questionable, but the unfavorable prognosis of such cases justifies it.

Quick, Bloodgood, Jungling, Pfahler (1938), and many others have advocated *preoperative irradiation* as a useful procedure. *As applied to operable cases, preoperative irradiation does not seem justified and has been abandoned by practically all clinics* (Adair, Haagensen, Harrington). Since the concept of operability in carcinoma of the breast should be dictated by experience rather than by the purely technical ability to remove the tumor, a large number of cases with a moderate local spread and with no evidence of distant metastases may be judged inoperable. It is possible that many of these borderline cases could be, if not more easily, perhaps more successfully operated following irradiation. Objections based on the pathologic examination of surgical specimens following radiotherapy are not entirely valid as an argument against preoperative radiotherapy, for the finding of viable tumor cells only means that the radiotherapy as applied has been unable to sterilize the tumor, but it does not disprove its

usefulness as an adjunctive measure. The different skills with which radiotherapy is applied and the different concepts of operability make a comparison of results practically impossible at the present time.

### Prognosis

The average duration of life for patients with cancer of the breast varies widely, but Dalund's analysis of 100 consecutively *untreated patients* is a reliable gauge: average duration of life, forty months (or 3.4 years), and the mean duration thirty months (or 2.5 years). Forty per cent of these untreated patients were alive at the end of three years, 22 per cent at the end of five years, 9 per cent at the end of seven years, and 5 per cent at the end of ten years (Fig. 675). This survey is of great value in judging the results of any particular type of treatment, for if treatment does not better this record it is worthless.

In carcinoma of the breast, the five-year survivals after surgery are considerably influenced by the type of lesion operated. Obviously if cases are taken which are not truly operable then five-year results will be extremely poor. Usually such statistics are made on the basis of those with axillary node metastases and those without. The number of cases falling in the first group depends on the thoroughness of the pathologic examination of the axilla. In evaluating the end results of carcinoma of the breast patients should not be excluded who have been lost to follow-up or who have died with intercurrent disease without evidence of cancer.

The additional study of five to ten-year statistics is useful because of the large proportion of late metastases (Fig. 676).

Table LXI illustrates the results which can be obtained and demonstrates the improvement on each succeeding five-year period. Carcinomas of the male breast have a much worse prognosis than carcinomas of the female breast. This is almost entirely related to the fact that when they are first seen they invariably present axillary lymph node metastases. Bilateral or simultaneous carcinomas of the breast have a prognosis which is also dependent on the presence or absence of axillary lymph node metastases. If the carcinoma is both bilateral and simultaneous the prognosis is much worse.

TABLE LXI. FIVE-YEAR SURVIVAL RATES FOLLOWING RADICAL MASTECTOMY FOR ADENOCARCINOMA OF BREAST. ONLY 151 CASES NOT TRACED AND NOT INCLUDED IN TABLE (From Harrington & W. Surgery, 1940)

PERIOD IN WHICH OPERATION WAS PERFORMED	WITH METASTASIS				WITHOUT METASTASIS				TOTAL SERIES		
	PA- TIENTS TRACED	LIVED 5 YEARS OF MORT AFTER OPERATION		PA- TIENTS TRACED	LIVED 5 YEARS OF MORT AFTER OPERATION		PA- TIENTS TRACED	LIVED 5 YEARS OF MORT AFTER OPERATION		NUM- BER	PER- CENT
		NUM- BER	PER- CENT		NUM- BER	PER- CENT		NUM- BER	PER- CENT		
1910-1914	90	71	77.7	12	12	100	51	61	78.4	113	78.4
1915-1919	386	115	29.8	292	211	72.3	88	376	42.3	489	42.3
1920-1924	550	155	28.2	76	25	32.9	1006	497	49.5	1557	49.5
1925-1929	750	245	32.7	705	705	100	1145	750	65.5	1895	65.5
1930-1934	71	213	300	70	34	48.6	1003	337	33.6	1376	33.6
1935-1939	4	178	44.5	408	221	54.2	803	112	14.0	1211	14.0
1940-1944	1518	101	6.6	151	151	100	1669	4	0.2	1819	0.2

The well-differentiated small tumor (2.5 cm or less) with no axillary metastasis has the best prognosis. If the tumor has extended to the axillary lymph nodes, the five-year survival rate immediately drops to 35 per cent or less, depending upon the number and location of the nodes involved and the degree of involvement of the soft axillary tissue. Clinical fixation of the tumor to the pectoral fascia may be disproved on pathologic examination. If microscopic

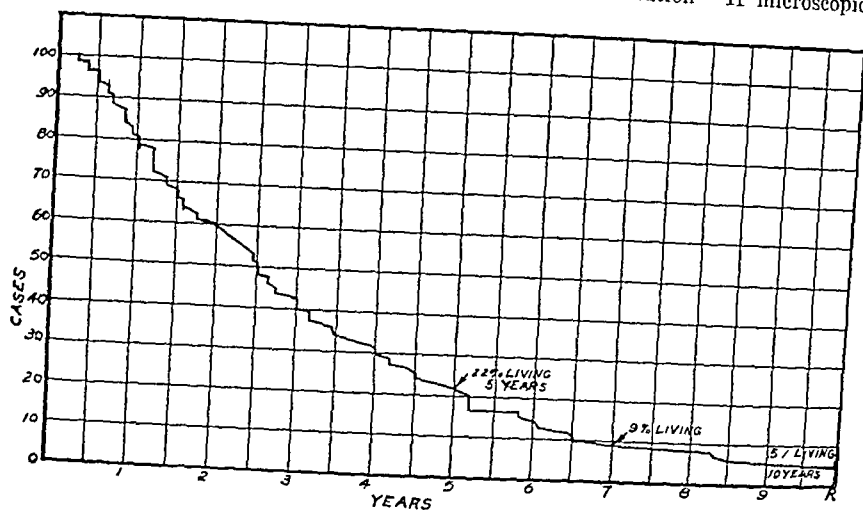


Fig. 675—Life expectancy of untreated cases of carcinoma of the breast (From Daland E. M. Surg. Gynec. & Obst. 1927)

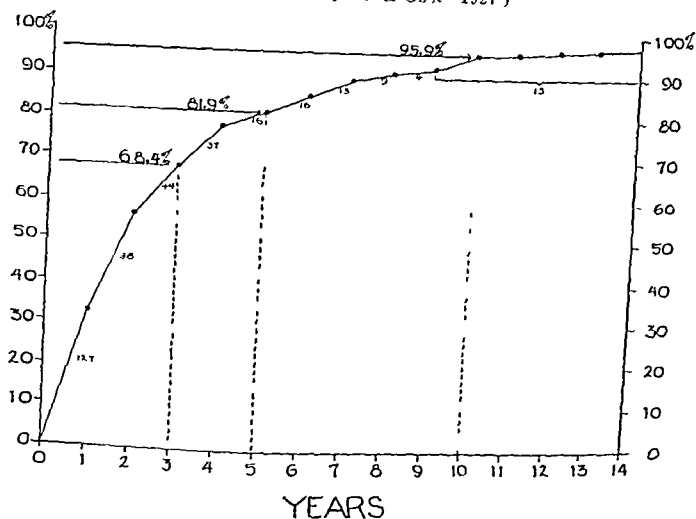


Fig. 676—A study of 793 failures of radical mastectomy for carcinoma of the breast. Fourteen per cent of these patients died between five and ten years following treatment (From Lewis D. Ann Surg. 1932)



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## Chapter XVI

### MALIGNANT TUMORS OF BONE<sup>\*</sup>

#### Anatomy

A knowledge of the fundamental development and histology of bone is necessary for an understanding of bone neoplasms. The long bones, which are most often the sites of primary tumors, are made up of two types—the compact and the spongy. The compact bone is a continuous sheath of bone in which no space can be observed except microscopically, while the spongy is made up of a latticelike network of bone. The bone is covered by periosteum which cannot be stripped away because of its strong attachment by Sharpey's fibers. Through the fibrous attachments of Sharpey's fibers, blood vessels and nerves extend into the compact bone. In the compact bone, the blood vessels create a rich network which is united to form the Haversian canals, which, in turn, communicate directly with the Volkmann's canals, penetrating through the periosteum.

The shaft of the bone is called the diaphysis, its extremities the epiphysis, and the portion of the shaft near the epiphyseal line is called the metaphysis (Fig 677). The epiphysis is made up of cartilage, but it becomes calcified at varying ages in the different bones. The degree of calcification depends on other factors. After calcification, the epiphyseal line is no longer a barrier to the spread of tumor, and therefore the age of the calcification is important.

The blood supply of the bones is of particular interest from the standpoint of metastases. The arteries enter the flat bones in various areas, and the veins leave these bones by separate canals. In the long bones, branches from the articular arteries enter the foramina at the extremities. The compact bone of the shaft is supplied by vessels running in the periosteum, and the walls of the medullary cavity and the medulla, by nutrient arteries. The nutrient arteries enter the medullary cavity through a special canal and divide into proximal and distal branches that anastomose with the articular arteries. The large veins of the medulla leave the bone through the same foramina that the nutrient artery enters.

**Lymphatics**—The lymphatics of the bones of the upper and lower extremity leave by the nutrient foramina, traverse the periosteum, and empty into the nearest deep collecting trunk. The lymphatics of the periosteum of the tibia terminate, for the most part, in the popliteal nodes but some empty into superficial inguinal lymph nodes.

#### Incidence and Etiology

The *giant-cell tumor* is included in the discussion of malignant neoplasms of the bone because, although it only infrequently undergoes malignant change,

<sup>\*</sup>Written with the collaboration of Dr. David V. LeMone.

of cells with marked mitotic activity, but very radiosensitive cells may not have a great reproductivity. The "law" of Bergonie and Tribondeau is of no help in the theoretic establishment of a scale of radiosensitivity of different tissues.

The intensity of the effects of irradiation and their permanency or permanence depend upon various intrinsic and extrinsic factors. Jolly demonstrated that the radiosensitivity of one half of the thymus in the rabbit is greatly affected by unilateral ligation of afferent vessels; thus he proved the importance of blood supply in radiosensitivity. The quality and quantity of radiations have an obvious bearing on the results; the greater the dose and the lesser the quality of the radiations, the less selective is their action and the more marked and diffuse are their effects, and the less reversible are these effects. The concentration or protraction of irradiations in time results in different effects.

The immediate reaction and the ultimate effect of radiations on the different tissues and organs greatly depend upon the quantity and character of radiations and the circumstances of their application; in addition, the effects produced upon the same type of tissue may be very different in two different animal species. This may lead to controversial experimental findings.

**Effects of Irradiation of the Skin**—The effects of irradiation of the skin are a singular example of radiophysiology; the knowledge of these effects is of great importance since the skin must be traversed in the treatment of deep-seated tumors and the reactions of the skin become an indicative and limiting factor in radiotherapy. The effects of irradiation on the skin vary greatly with the *dose delivered*, the quality of radiations, the size of the irradiated area, the region of the body, and the individual idiosyncrasy. The quality of radiations and the size of the field have an important bearing on the *dose absorbed* by the skin. The intensity of the immediate reaction is greater, all other conditions the same, the shorter the time in which the total dose is delivered; the late effects vary according to the protraction of the total dose and individual idiosyncrasy.

The administration of radiations to the skin may result in an immediate rubicundity or flushness which usually disappears after a few hours. With a moderate dose the hair falls or is easily drawn after ten to fourteen days. A larger dose results toward the third week in the development of an erythema which becomes brighter and later may turn to brown. The elimination of large scaly fragments of epidermis underneath which there is a new thin skin known as a *dry epidermitis*, may occur between four and five weeks following a single irradiation. With the administration of a somewhat larger dose (or with a larger field, or inferior quality of radiations), the erythema ends at three to four weeks in a denudation of the dermis, with or without previous formation of vesicles in what is known as a *moist epidermitis* (Regaud, 1913). This denuded area weeps constantly and is subject to easy secondary infection. It is rapidly covered within a few days by the development of confluent circular islands of new epidermis arising both from the center and borders of the area (Figs 16 and 17). A more intense radioepidermitis takes a considerably longer period to repair since the epidermis may only grow from the borders of the area. A





relatively insignificant trauma often cited could possibly cause this neoplasm. Jaffe saw an early osteogenic sarcoma in a patient who had had a recent trauma, and if a roentgenogram had not been taken at once, this case would have erroneously fulfilled the criteria for a traumatic osteogenic sarcoma (Stewart). Sarcomas of bone have been produced experimentally by means of *roentgen rays* and *radium*. Lacassagne produced fibrosarcoma of the tibia in a rabbit thirty-six months after 1 980 roentgens had been administered to an abscess near the bone. Dunlap reported osteogenic sarcoma in the vertebrae and pelvic bones of rats which had been fed small amounts of radium. The average time interval from ingestion of radium to appearance of the tumor was one year. Hatcher collected twenty-seven cases of bone sarcoma which developed in apparent connection with the local administration of large amounts of radiations. The interval between the treatment and the appearance of sarcoma was invariably long, the average being six years. Chondrosarcomas developed more frequently in this group than did other bone tumors.

Martland reported a series of eighteen patients who died from *radium* poisoning, five of whom had developed osteogenic sarcoma. The victims were young women employed in the painting of clock dials with a luminous paint made of zinc sulfide and 1 part in 40 000 of radium, mesothorium, and radiothorium. It was the custom of the workers to moisten the bristles of the brush between their lips and this resulted in the ingestion of a certain amount of radioactive material.

There is no doubt that Paget's disease has a definite relationship with osteogenic sarcoma. It is estimated that 7.5 per cent of all cases of Paget's disease eventually develop osteogenic sarcoma. When osteogenic sarcoma develops on the basis of Paget's disease, it occurs in the areas where Paget's disease is most advanced and usually has been present for ten to fifteen years (Coley). Osteogenic sarcomas of the skull almost always occur in males suffering from Paget's disease. Paget's disease preceded the development of osteogenic sarcoma in 28 per cent of seventy-one patients over the age of 50 years; these cases were collected from the Memorial Hospital and the Bone Tumor Registry. Men are affected five times more frequently than women. Both osteogenic sarcoma and Paget's disease are rare conditions and the fact that they are associated is significant, not coincidental (Coley). In Coley's group, no patient under the age of 50 years had osteogenic sarcoma associated with Paget's disease. Multiple osteogenic sarcomas arise only rarely on the basis of Paget's disease (Kienboek).

*Chondrosarcomas* are considered separately from osteogenic sarcomas because their clinical behavior, pathology, treatment, and prognosis are distinctive. They may arise from pre-existing enchondriomas. In multiple cartilaginous exostosis (chondrodysplasia), the chondrosarcoma arises from the cartilaginous cap of the exostosis. If these cases of chondrodysplasia are followed long enough, a fairly good number will develop chondrosarcoma (Jaffe). *Multiple myeloma* occurs in males in about 70 per cent of instances has a peak age incidence of 55 (about 50 per cent occur between 40 and 70 years). *Reticulum cell sarcoma* of bone is rare, occurs with equal frequency in males and females, and about 85 per cent of the cases occur after the age of 40 years (Jackson).

it is one of the common bone tumors. It occurs predominantly in patients between 20 and 35 years of age and is more often found in females than in males. *Ewing's sarcoma* makes up 7 to 15 per cent of all malignant bone tumors and predominates in males in a ratio of 2 to 1. Meverding (1938) reported 114 cases, of which 72 per cent were in males and 28 per cent in females. This tumor is infrequent after the age of 30 years. Ninety-five per cent of Copeland and Geschickter's (1930) patients were between 4 and 25 years of age, and seventy-six of 114 patients reported by Meverding were less than 30 years old. There is a history of trauma in about 35 per cent of the cases, but there is no proof that trauma plays an etiologic role.

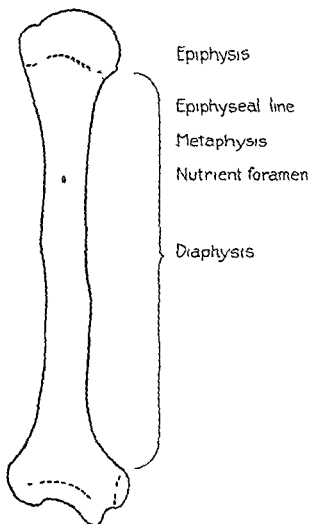


Fig. 6 —Sketch of a humerus identifying the different anatomic landmarks in a long bone

*Osteogenic sarcomas* make up about 30 per cent of all malignant bone tumors. They predominate in the male and are most common between the ages of 10 and 30 years, although they may occur in older individuals particularly in males. A traumatic etiology of bone sarcoma remains unproved (Stewart). Major trauma (fracture, surgery, particularly amputation, and exodontia) does not cause osteogenic sarcoma. It is difficult to understand, therefore, how the

tion to the tumor rather than a specific product of it. With further growth, the tumor spreads to involve a greater portion of the shaft and finally extends through the periosteum into the soft tissue. This involvement of the shaft is characteristic and widespread involvement is the rule (Fig 679). With separation of the periosteum, spicules of new bone from the subperiosteal layer are laid down at right angles to the shaft. These changes occur because Volkmann's canals unite the periosteal blood supply with the Haversian vessels. The tumor frequently shows areas of hemorrhage, cyst formation, and rarely zones of necrosis and inflammation.

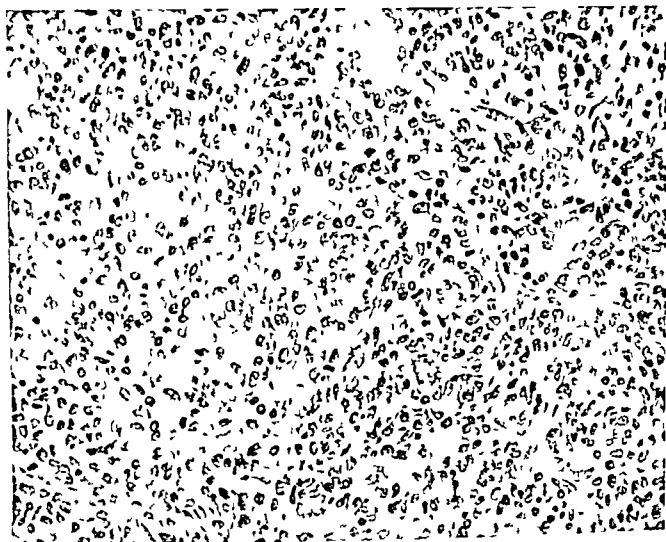


Fig 678—Photomicrograph of a giant-cell tumor showing numerous giant cells with multiple regular identical nuclei. Stroma reveals increased cellularity but the individual cells are uniform (moderate enlargement).

On microscopic examination Ewing's sarcoma is made up of broad sheaths of tumor with polyhedral-shaped cells with very scanty or pale cytoplasm. The individual cells are monotonously similar with small nuclei and fine nucleoli (Fig 680). There is no intercellular substance and *the tumor never produces osteoid*. The Haversian canals are frequently infiltrated. The exact histogenesis of these tumors remains obscure, although some authorities consider that they are probably derived from young reticular cells (Oberling, Stout, Lichtenstein).

The gross appearance of an *osteogenic sarcoma* is exceedingly variable and depends upon bone production, vascularity, extent, and duration of the lesion. These tumors most commonly begin in the metaphysis of long bones. In about 70 per cent of the cases, the tumor arises in the bones of an extremity. The sites of predilection in order of frequency are femur, tibia, humerus, bones of the pelvis, fibulas, the bones of shoulder girdle, bones of hand and foot, ribs, jaws, and vertebrae. About half of all the cases of osteogenic sarcoma are found in the femur, and in four of every five of these the tumor arises in the distal end

## Pathology

**Gross and Microscopic Pathology**—A tentative classification of bone tumors is found in Table LXII

TABLE LXII TENTATIVE CLASSIFICATION OF BONE TUMORS DEGENERATIVE DISEASES, QUESTIONABLE AND HYPOPLASTIC NEOPLASMS AND METASTATIC LESIONS ARE NOT INCLUDED

BENIGN	MALIGNANT
Osteoma	Osteogenic sarcoma {Sclerotic Osteolytic
Osteoid osteoma Osteochondroma	Chondrosarcoma {Peripheral Central
Chondroma	
Chondroblastoma	
Giant cell tumor	Giant cell tumor (Rare)
Plasmacytoma (?)	Myeloma
Lipoma	Liposarcoma (?)
Fibroma	Fibrosarcoma {Periosteal Marrow
Hemangioma	Hemangioendothelioma
Neurofibroma	Ewing's sarcoma
Myxoma	Histiocytoma cell sarcoma

*Giant cell tumors* arise in the epiphyseal end of the long bones from the undifferentiated supporting connective tissue of the marrow. They are most frequent in the lower end of the femur, the radius, and the upper end of the tibia. They can occur, however, in numerous other bones: ulna, ribs, metatarsus, patella, fibula, vertebrae, maxilla, and pelvic and metacarpal bones. This tumor is globular in shape, has a well defined capsule, is traversed by connective tissue bands, and contains numerous loculated, well vascularized spaces. The larger tumors thin out the cortex and infrequently fracture. They do not affect the joint or cause periosteal reaction. A relatively small proportion of giant cell tumors become malignant (Simmons, Stewart, Jaffe). Microscopic examination reveals the tumor to be made up of two elements: stroma and giant cells (Fig. 678). The giant cells are presumably products of fusion of nuclei from the stromal cells. Many of these giant cells contain twenty to thirty five nuclei identical in appearance. The prominence of these giant cells under the microscope has given them an unprecedented importance. The stroma, however, is of much greater importance and should be carefully examined from the standpoint of cellularity, mitotic activity, and variation. Jaffe has set up criteria for the grading of giant cell tumors in order to facilitate treatment.

*Ewing's sarcoma* occurs most frequently in the femur, tibia, mandible, humerus, fibula, and pelvic bones (Geschickter and Copeland) and can also appear in the ulna, clavicle, metacarpal, radius, ribs, vertebrae, and bones of the metatarsus and skull (Rix). In seventy of 114 cases reported by Meyerding (1938), the tumor occurred in an extremity. In the long bones these tumors take origin in the shaft and never primarily involve the epiphysis. In the early stages there is condensation of the shaft of the bone and the widened cortex is made up of subperiosteal and endosteal formation of new bone. This new bone is a reac-

tumor usually involving the end of a long bone (Fig 693) The tumor is made up of dense connective and osteoid tissue It will usually have extended through the periosteum to involve the surrounding soft tissue and muscle (Fig 695), and it may have extended down the marrow cavity without, however, having involved the joint cavity The predominantly osteolytic tumor may be cut with ease and may present large areas of hemorrhage and necrosis Fragmentation of the periosteum and invasion of the soft tissues are early phenomena in this type of tumor (Plate IX) Osteogenic sarcomas invade the epiphysis after ossification of the epiphyseal line has taken place, and they may involve the joint secondarily after fracture or perforation of the periosteum in the metaphyseal region (Plate IX) In many instances there may be laying down of bone at right angles to the shaft because of extension of the tumor beneath the periosteum The periosteum confines the tumor and gives it a spindle shape which is altered if the neoplasm grows through it

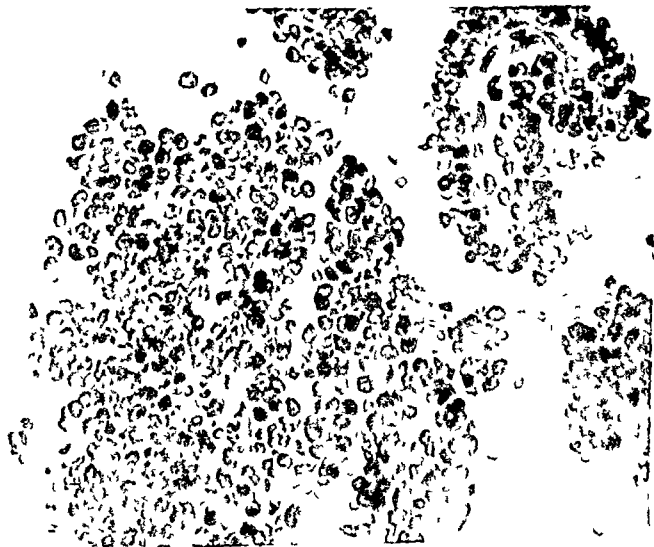


Fig 680—Photomicrograph of an Ewing's sarcoma showing uniformity of individual cells with scanty cytoplasm and fine nucleoli No osteoid is present (moderate enlargement)

Pack has reported five patients in whom the bony tissue of *myositis ossificans* underwent neoplastic alteration to become osteogenic sarcoma This lesion develops in the muscles around their insertions, and the changes take place primarily within the fascial connective tissue The lesion may occur as a localized area following slight injury, irradiation, or a single trauma, or it may develop without cause There is a rare type beginning in the muscles along the spine which spreads to involve all the muscles of the body

The microscopic appearance of osteogenic sarcoma is extremely variable and differs from area to area (Fig 681) If large or multiple sections are taken,

of the bone The distal end of the humerus and tibia rarely gives rise to osteogenic sarcoma (Kolodny) In the shoulder girdle, the scapula is the seat of predilection The large bones of the foot may also be the site of an osteogenic sarcoma, but involvement of the phalanges of fingers and toes is unusual

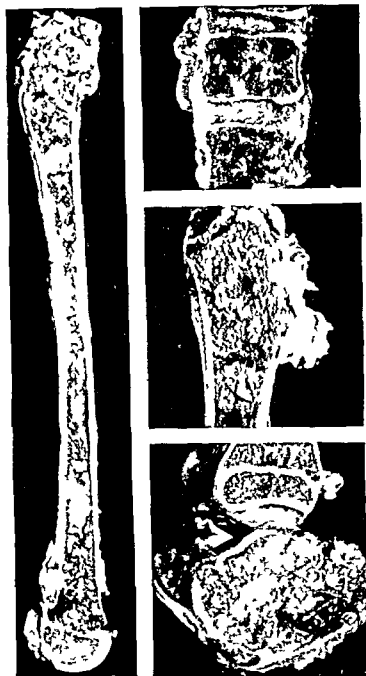


Fig 679—Widely disseminating Ewing's sarcoma with extensive replacement of the bone marrow while the cortex of the bone remains relatively unchanged This tumor first arose in the os calcis (From Kolodny *J Surg Gynec & Obst.* 1947)

Osteogenic sarcomas are sometimes divided into sclerosing and osteolytic varieties but all gradations of each occur and one blends into the other The cut section of a predominantly sclerosing osteogenic sarcoma shows a fan shaped

## PLATE IX

Sclerosing type of osteogenic sarcoma of the femur with extensive involvement of the metaphysis and shift and invasion into the ossified epiphysis. Same patient as in Fig. 690.

Osteolytic hemorrhagic osteogenic sarcoma of the metaphyseal region of the tibia with fragmentation of the periosteum and extension into the soft tissue. The epiphysis is cartilaginous and therefore not invaded.

Chondrosarcoma of the upper end of the femur with fracture and extension down the shaft and into the soft tissues.

Cross section of typical chondrosarcoma.

Osteochondromatous lesion of the rib simulating osteogenic sarcoma with expansion within but no extension outside of the bone.

Extrasosseous osteogenic sarcoma—soft tissue of the thigh.

the variation is more apparent. There is, therefore, little justification for any complicated classification, for fundamentally speaking, the osteogenic tumor arises from bone forming mesenchyme which can give rise to spindlelike cells, mucoid material, cartilage, and bone. In the typical osteogenic sarcoma, osteoid tissue is usually seen evolving directly from a sarcomatous stroma. *This does not occur in the chondrosarcoma.* The presence of giant cells and well-differentiated fibrous areas may be confusing. In our experience periosteal fibrosarcoma is rare. In a few instances true medullary fibrosarcomas can occur.

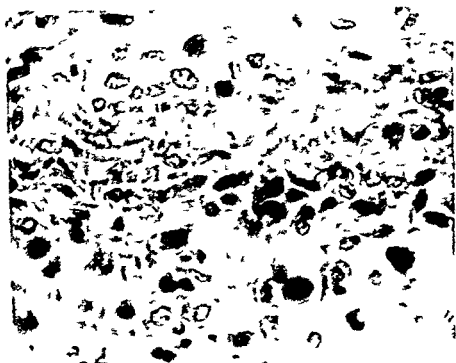


Fig. 661.—Extremely undifferentiated osteogenic sarcoma with innumerable bizarre cellular forms (high power enlargement).

*Chondrosarcomas* are less common than osteogenic sarcomas and should be separated from them. These neoplasms arise from full fledged cartilage (Jaffe). They arise centrally from enchondromas or from the cartilaginous cap of an exostosis. Enchondromas arising in the small bones however, practically never show malignant degeneration. In multiple cartilaginous exostoses, an entity which is better designated as chondrodysplasia (Ehrenfried, Keith), chondrosarcoma frequently arises (Fig. 701). In Jaffe's twenty-eight patients, three showed malignant transformation in one or more exostoses. He believes that the true incidence is actually much higher, because so often the lesions of chondrodysplasia are found first in childhood or adolescence, but malignant transformation does not take place until years later. Chondrosarcomas occur most frequently near the ends of long bones and produce an expansile swelling of the shaft. They often extend within the marrow cavity, but eventually may break through the bone, produce fractures and grow into the soft tissue (Plate IX). It is usually difficult to be certain whether the tumor arises from a pre-existing





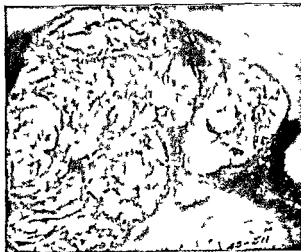
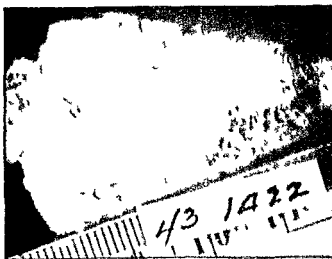


PLATE IX



Fig. 1—Mo. radiograph showing a large area of epidermal nevi at the bottom and center.



Fig. 1"—Mo. radiograph of the pubic skin following roentgentherapy for carcinoma of the cervix.

enchondroma. However, in the tumors arising from the cap of cartilaginous exostoses the primary lesion may be recognizable either by roentgen examination or at gross examination, and often there are other stigmas of chondrodysplasia. Pheemister's ten cases of chondrosarcoma were distributed as follows: three in the femur, two in the humerus, two in the tibia, and one each in the maxilla,

Fig. 682

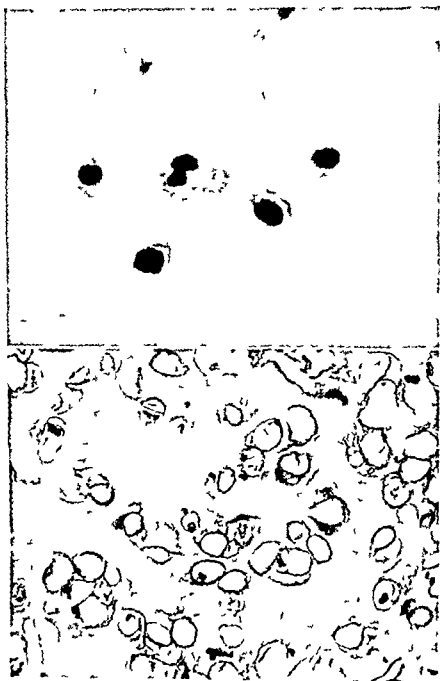


Fig. 683

Fig. 682 —Photomicrograph of a chondrosarcoma showing multinucleated cells and plump nuclei (moderate enlargement)

Fig. 683 —Photomicrograph of a chondroma with no multinucleated forms and very regular pattern. Note contrast with previous photomicrograph (moderate enlargement)

spine, and rib. No matter the location, these tumors tend to grow to a large size, particularly when they are located in the pelvis or upper femur. On section they often contain small spicules of bone and show numerous cystic spaces which contain glairy mucoid material (Fig. 703). Very frequently at gross examination, tumor invasion of large veins can be seen.

Microscopically, chondrosarcomas are made up of cartilage cells, and often it may be difficult to tell whether they are benign or malignant. Jaffe (1943) stated that if enough sections were examined, the chondrosarcoma would show cells with multiple nuclei, plump nuclei, abnormal nuclei, or mitotic figures (Figs. 682 and 683). In our experience these changes are not invariably found



Fig. 684—Photomicrograph of a plasma-cell myeloma. Note typical cells with eccentric nuclei, "wheel" arrangement of the chromatin, and one multinucleated form (high power enlargement).

The *myeloma* most frequently involves flat bones, ribs, vertebrae, pelvis, and skull. This tumor tends to produce extensive areas of patchy destruction. The involved bone may have a preserved paper-thin cortex. At necropsy, the entire vertebral column may be so soft that it can be cut with a knife. The areas of destruction are more often patchy than diffuse and zones of hemorrhage, infarction, and necrosis are not unusual. The tumor is usually grayish-red in color. At times this tumor may be first seen as a single focus within a flat bone or in the pelvis, vertebra, or femur. The widespread replacement which is often seen in the end stages may be due to multiple foci of origin.

Microscopically the examination of the bone shows diffuse replacement by tumor cells. In the vertebrae this results in destruction of the bony framework and complete replacement by tumor. The characteristic cells have been divided into four types by Ewing: the plasma cell myeloma, myelocytoma, lymphocytoma, and erythroblastoma. The exact histogenesis of the plasma cell is un-

known although it may be of reticuloendothelial origin. The other three types are derived from leucocytes, lymphocytes, and nucleated red cells. These subdivisions are of interest to the pathologist but have little practical significance to the clinician. The plasma cell variety is the most common and the individual cells have eccentric nuclei with a cartwheel arrangement of the chromatin (Fig 684). Frequently they are multinucleated and their cytoplasm is pink with a perinuclear halo.

All other malignant tumors of bone are rare. Primary *reticulum cell sarcoma* of bone was first described by Oberling and later by Jackson, who reported twenty-five cases. The tumors occurred in patients of all ages and, for the most part, were in long or flat bones, particularly femur, clavicle, tibia and humerus. In the long bones, the tumor begins in the metaphysis and extends to involve a large area of the diaphysis. The medullary cavity is often extensively invaded by pinkish gray tissue which in advanced stages, is accompanied by areas of bone destruction. Areas of necrosis are frequent (Parker). *Liposarcomas* (debatable tumors of bone) have been reported arising from the femur, fibula, and radius (Stewart). About fifteen cases of *ameloblastomas* of the tibia have been reported, occurring in equal proportion in males and females. The youngest patient reported by Hebbel was 12 and the oldest 57 years. These tumors arise in the tibial shaft and usually involve the subperiosteal cortical portions. They often extend into the medullary cavity and may grow out into the soft tissues. The epiphysis is not invaded. The histogenesis of these probably heterotopic tumors is uncertain but microscopically they resemble the *ameloblastoma* seen in the maxillas. Rare malignant tumors of blood vessel origin (*hemangioendothelioma*) have also been reported (Fienberg).

**METASTATIC SPREAD**—*Giant cell tumors* do not metastasize except in the few rare instances when they become malignant and then most often to the lungs. *Ewing's sarcomas* metastasize early and widely and the distribution of metastases is characteristic. The lungs, lymph nodes and bones of the skull in this order are most frequently involved. Widespread bone metastases may occur in the skull, spine, scapulas and clavicles; this ability to metastasize to other bones is unique, and it is still a questionable point whether the bone lesions represent metastases from the primary lesion or whether they represent multiple foci of origin. *Osteogenic sarcomas* and *chondrosarcomas* do not metastasize to lymph nodes. *Osteogenic sarcoma* primarily spreads by blood vessels most often to the lungs. The *chondrosarcoma* very characteristically grows into the large veins. These tumor thrombi may extend over long distances from the femoral vein even as far as lungs (Warren Kosr). *Multiple myeloma* is invariably discovered only after it has spread to many bones. Those most frequently affected are the vertebral bones of the pelvis, the skull, the ribs, clavicles, and sternum. Infrequently lymph nodes, spleen, liver, and other organs can be implicated. Pulmonary metastases are rare.

### Clinical Evolution

*Giant cell tumors* begin insidiously, their first symptoms usually suggest a mild arthritis or neuritis and later definite local pain may appear which produces increased disability. The very large giant cell tumors occurring in the

lower end of the femur or tibia may cause complete disability. Fractures may occur in the weight-bearing bones (10 to 15 per cent). These tumors alone rarely cause death. In rare instances death may come when an inadequately treated giant-cell tumor becomes malignant and disseminates.

The first symptom of *Ewing's sarcoma* is often pain, which almost invariably appears at some time during the course of the disease. The tumor usually makes its clinical appearance with the pain, and, in fact, tumor without pain is unusual. The pain is deceptive and intermittent. It may disappear with exercise and for that reason is often considered of no significance. As the disease progresses, the attacks of pain become more frequent and intense. It is usually more severe at night and is accompanied by fever ranging from 99 to 103° F. This elevation of temperature is somewhat proportional to the duration of the tumor and its size.

Radiotherapy dramatically stops the pain, but it may recur shortly in new areas. With the dissemination of the disease to regional lymph nodes, other bones, and the lungs, the patient becomes extremely emaciated and often dies of some complication such as bronchopneumonia.

The onset of *osteogenic sarcoma* often resembles rheumatism, a sprain, or arthritis. The pain is minimal in most instances and precedes the appearance of tumor by days, weeks, or months. It is undoubtedly due to the tension placed on the periosteum by underlying tumor and may abruptly be alleviated if rupture of the periosteum occurs. In the lower extremities it may be relieved by drawing up the legs and thus relaxing the muscles overlying the taut periosteum. As the tumor increases in size, the pain becomes severe and worse at night, which contributes in some degree to the progressive weight loss. Osteogenic sarcomas have a variable speed of growth, the osteolytic varieties developing much more rapidly than the sclerosing types. The osteolytic type of tumor causes elevated temperature with increase in pulse rate. If the tumor is not treated, then dissemination of the disease to the lungs takes place, followed by further dissemination, extreme weight loss, and death. The clinical evolution of the *chondrosarcoma* does not differ from that of the other osteogenic sarcomas except for a slower growth rate.

The first symptoms of a *multiple myeloma* are intermittent, usually in the form of local pain, suggesting neuralgia and arthritis. This pain often becomes worse with exercise. As the disease progresses and disseminates, there may be episodes of extreme pain followed by collapse. Fracture is common in this type of bone tumor and occurred in approximately 20 per cent of the patients with multiple myeloma reported by Meierding (1941). Paraplegia may be the first sign of disease because of collapsed vertebrae. The fractures often occur in nonweight-bearing bones, appearing most frequently in the ribs, usually between the fifth and twelfth. A multiple myeloma may begin as an extramedullary tumor, to be followed later by multiple bone lesions (Hellwig). In still other instances the tumor begins as a single focus within a bone, such as vertebra, clavicle, or femur, and causes local pain. Treatment of one of these areas may relieve the symptoms, but years later there may be widespread dissemination. In the late stages of multiple myeloma, there is excessive pain due to multiple

fractures, and also extreme weight loss and anemia. Thoracic deformities, kyphosis, and shortening of stature due to the involvement of the vertebra may also develop. Renal failure due to tubular changes specific to multiple myeloma can occur (Snapper). Pulmonary complications are common.

The *reticulum-cell sarcoma* of the bone usually begins with pain localized to the site of the disease. As the process continues, the pain becomes more and more prominent and weight loss ensues. The tumor often grows rather slowly and dissemination of the disease may take three years to develop.

### Diagnosis

*The diagnosis of bone tumor requires the combined efforts of an experienced clinician, roentgenologist, and pathologist.* If the clinical history and examination are deficient if roentgenograms are of inferior quality or badly interpreted if biopsies are poorly prepared and the histologic opinion is not expert, then an accurate diagnosis is seldom made. The clinical history must be carefully taken from the viewpoint of exact time of onset, presence or absence of pain, fever and rate of growth of the tumor. The clinical examination should estimate the exact limits of the tumor and its relationship to the bone, joint and skin. The presence or absence of increased vascularity and the relationship of the tumor to the surrounding muscles should be ascertained. Roentgenograms must be carefully taken, several views may be necessary. The pathologist should report only on well selected and well prepared biopsies. When all this information is put together an accurate diagnosis can usually be made. Efforts to make a diagnosis on just clinical, roentgenographic or pathologic grounds alone often result in errors.

Once the presence of a bone tumor is established, there are further identifying factors which are not, however, absolute. The age of the patient may help in diagnosis. Giant cell tumors are most frequently observed in patients 20 to 35 years old. Ewing's sarcomas are very infrequent after the age of 30 years. On the other hand myelomas practically never develop before 40 years. The majority of osteogenic sarcomas appear between 10 and 30 years of life. Like multiple myelomas they can occur in aged patients in which case they are often associated with Paget's disease. The sex of the patient may have a slight bearing on the diagnosis. The giant cell tumor is more often found in females than in males, Ewing's sarcoma, osteogenic sarcoma and multiple myeloma predominate in males. A knowledge of the usual distribution of bone tumors in the skeletal system is of relative value (Fig. 685). The location of a tumor in a long bone is also of differential value in that the giant cell tumors of the long bones occur in the epiphysis, the Ewing's sarcoma in the shaft, the osteogenic sarcomas in the metaphysis and multiple myelomas in the shaft.

The giant-cell tumor may show areas of tenderness at local examination but usually there is no increased temperature of the skin and no dilated veins. It may have a bulky, spherical shape, and a gush of crackling may be present on palpation. In the very vascular type a bruit may be heard. A Ewing's sarcoma of the long bones often forms a fusiform mass over the involved shaft. The temperature of the overlying skin is increased and small superficial blood vessels



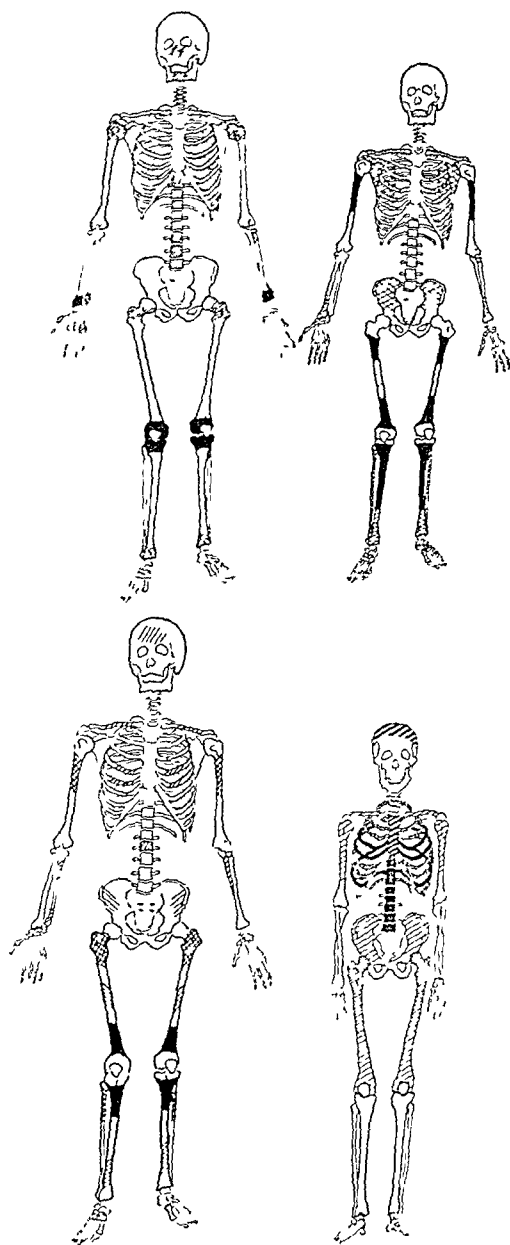


Fig. 685.—Common distribution of giant-cell tumors (upper left) of Iwima's sarcoma (upper right) sclerosing osteogenic sarcoma (lower left) and multiple myeloma (lower right). The solid black areas indicate the most common sites of origin, the checked areas the fairly common locations, and the diagonal lines the occasional sites. (From Geschickter, C. F. and Copeland M. M. Am J Cancer 1936.)

are often prominent. The skin moves freely over the surface of the tumor but on pressure exquisite pain is elicited. Evidence of fracture is infrequent. In the rapidly growing *osteogenic sarcoma*, the tumor mass often is relatively small, the temperature of the overlying skin (bluish red) is elevated, and pain may be very marked with movement. Any factor which produces tension on the periosteum results in increased pain. With the osteolytic variety, vascularization is rich and pulsation of the tumor mass can often be felt. Dilated superficial veins may be present. The larger tumors stretch the skin taut but do not ulcerate it. A *reticulum cell sarcoma* is suggested when the tumor is of slow growth and the patient is young and in relatively good condition in spite of advanced local disease. Usually, however, the diagnosis is not made until biopsy is done.

#### Roentgenologic Examination —

Roentgenographic examination of *giant cell tumors* reveals a well delineated cystic lesion with abrupt transition from normal bone. As the tumor grows in the long bones the involved area becomes club shaped. There is usually no periosteal thickening (Fig 686). A fine irregular network of trabeculation may traverse the tumor, but in some instances only osteolysis is apparent (Fig 687). Baclesse emphasizes that in the growth of the tumor there is a peripheral advance of osteolysis followed by a period of recalcification. These phenomena may take place three or four times in eight to twelve years, producing an effect described as an "accordion like tumor." The osteolytic phase may give an erroneous impression of malignant change. Changes in the bony architecture following curettage and roentgentherapy may be confusing so that a knowledge of these changes is of value in describing follow up roentgenograms (Brunschwig). If fracture occurs in a weight bearing bone, the fragments are telescoped.

In *Ewing's sarcoma* the earliest alterations are seen in the marrow cavity with differences in density due to breakdown of architectural framework. Slight roughening of the periosteum may be observed and this may lead to the erroneous diagnosis of osteomyelitis. As the process continues the tumor extends parallel to the long axis of the bone and involves more and more of the shaft (Fig 689). Because these changes are so evenly distributed, the pathologic findings often show more involvement than the roentgenologic examination reveals. There may also be an accentuation of changes in the cortical bone and periosteum without much change in the shaft. These changes are due to permeation of tumor cells through the Haversian canals (Swenson). An apparently normal marrow shadow does not rule out the possibility of a central origin. When the tumor has become extensive, endosteal defects occur and marrow abnormalities become apparent. According to Swenson additional evidence of the central origin of a *Ewing's sarcoma* is found when the metaphysis of a long bone is affected and the involvement of the cancellous bone in the subepiphyseal zone occurs simultaneously with the involvement of the thin cortex and the subperiosteal space in this region. In twenty six patients with *Ewing's sarcoma* reported on by Swenson bone destruction was revealed in twenty four,

increased density within the bone in five, increased width in eight, subperiosteal new bone in eleven a layering effect in four and a prominent soft tissue mass in seven. Varying amounts of periosteal thickening may be present and some times accompanied by a lamellar deposit and subperiosteal new bone of so called onionskin appearance. This onionskin feature often considered as diagnostic is inconstant. In Swenson's series it occurred in only four of twenty-six cases. As the tumor grows the medullary cavity reveals extreme osteoporosis and the cortex shows prominent evidence of bone destruction. The periosteum becomes separated and new bone is laid down at right angles to the shaft. At times a Ewing's sarcoma may simulate a soft tissue sarcoma because of apparent absence of bone changes (Potozky).



FIG 686

FIG 687

FIG 686—Grant-cell tumor of the lower end of the femur showing a characteristic mottled appearance and no evidence of periosteal reaction.

FIG 687—Grant-cell tumor in the epiphyseal region of the upper end of the tibia with sharply delineated osteolytic appearance and without periosteal reaction.

In *osteogenic sarcoma* the variable changes are a reflection of the summation of changes rather than an indication of specific tumor type. The sclerosing type of osteogenic sarcoma is much more common than the osteolytic, and the tumor may be either peripheral or central. The peripheral type is classic, with Cod

man's reactive triangle (elevation of periosteum) (Fig 691), dense obliteration of cortical striae secondary destruction of the medulla and mottled areas. The osteolytic variety shows irregular expansile destruction of cortex varied periosteal reaction, early perforation and a bulky mass (McDonald). As the tumor increases beneath the periosteum, needlelike new bone may be observed growing at right angles to the shaft. The presence of new bone parallel to the long axis is thought by some to be diagnostic of osteogenic sarcoma. These



Fig 688 —Extremely large giant cell tumor of the upper end of the tibia of long duration. The tumor has extended into the soft tissue. This type of lesion may result in fracture.

changes represent fairly advanced disease. New bone can be deposited in any process neoplastic or inflammatory which causes elevation of the periosteum; we have seen it in tuberculosis, in syphilis and in metastatic neoplasms (Figs 709 and 710). The epiphysis of the long bones is never invaded by osteogenic sarcoma, unless the epiphyseal cartilage has become ossified (Figs 690 and 691). In advanced stages the osteogenic sarcoma may take on a reputed characteristic

sumary appearance a configuration modeled by the periosteum. After the tumor breaks through the periosteum the pattern is altered again as the tumor speedily grows in the surrounding structures. There is a variable degree of osteolytic change within the involved bone combined with a variable amount of osteoplastic changes. In the advanced stages, fractures may infrequently be seen in the weight-bearing bones particularly in the osteolytic varieties. Metastatic



Fig. 680.—I wing's sarcoma arising in the shaft of the tibia without involvement of the epiphysis. Note increased density in the medullary portion of the bone with subperiosteal new bone formation and a soft tissue mass.

osteogenic sarcoma in the lungs is often preceded by roentgenologic evidence of pleural effusion due to pleural involvement, later the lungs may be packed with innumerable spherical homogeneous nodules.

The *chondrosarcomas*, for the most part, either arise from pre-existing enchondroma (central type) or from a cartilaginous exostosis (peripheral type)

larger dose may result in bleeding from the dermis followed by secondary infection and loss of substance, which is known as *acute radiodermatitis*, a true radionecrosis of the dermis which is not reparable unless it is very limited.

The *permanent sequelae* resulting from irradiation of the skin are also varied. With a small dose the epilation produced is only transitory, but when a radioepidermitis has been produced, the epilation is usually permanent. Except for epilation there may be little visible sequelae even after a radioepidermitis, but achromia, fibrosis, atrophy, and telangiectasis may gradually develop in very variable degrees (Fig 18), depending on intensity, the region, idiosyncrasy, etc. An intense radioepidermitis with long period of repair may give place to a discolored atrophic skin which becomes dryer and less pliable (Fig 19) and may easily break down years later (spontaneously or following trauma and secondary infection), the result is a necrotic ulceration, a *late radiodermatitis*, the development of which may be due as much to a lack of local vitality as it is to trauma and infection.



Fig 18—Slight achromia and atrophy of the skin of the face several years after roentgen therapy for a carcinoma of the upper maxilla.

The *radiobiologic mechanism* of skin reactions is one of the best examples of selective cytotoxic effect of radiations. Beyond a certain minimum dose the administration of a single dose of radiations may destroy the life of the cells of the germinal layer of the epidermis and hair follicles all or most of which die immediately or shortly afterward in abortive mitoses. The irradiation has very little if any effect on the more superficial cells of the epidermis; the hair stops

a cystic trabeculated appearance resembling a giant-cell tumor (Gootnick). It can also show a frankly osteolytic process. The ilium, femur, humerus, and thoracic vertebrae are the most frequent sites of a single myeloma.

The roentgenographic appearance of a primary *reticulum-cell sarcoma* of bone is not characteristic. It is chiefly an osteolytic process involving the metaphysis and extending to involve the diaphysis. In the early evolution



Fig. 691.—Osteolytic, rapidly growing osteogenic sarcoma of the upper end of the tibia in a girl 15 years of age. The tumor arose in the metaphysis and shows no invasion of the still cartilaginous epiphyseal line. There is fragmentation of the periosteum and the formation of a large soft tissue mass. Codman's reactive triangle is clearly defined (See Plate IX, Fig. 2 for gross specimen).

of the process the only changes may be mottled areas of bone destruction within the medullary cavity. Later fragmentation of the cortex and widening of the shaft may be present. Periosteal thickening is seen both early and late in the disease, and invasion of surrounding soft structures is not unusual (Jackson).

The central chondrosarcomas arise from the femur and humerus or in the region of the metaphysis and show blotchy or scattered small areas of calcification (Pendergrass). In the long bones they produce an expansile swelling of the shaft which results first in thickening of the cortex. The tumor may become very large and often there are cystic spaces within it (Fig 700). Blotchy areas are particularly characteristic (Fig 702). In peripheral chondrosarcomas there are often other lesions indicative of chondrodysplasia.

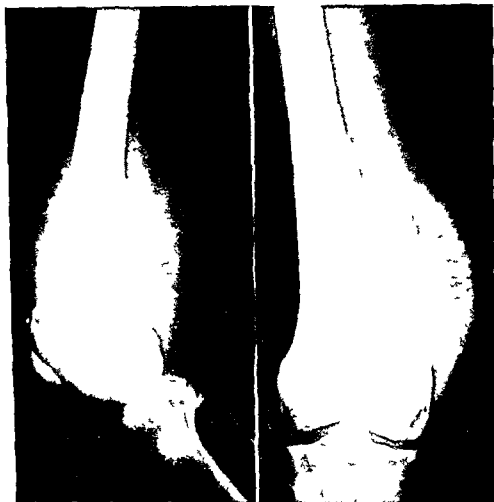


Fig 690.—Sclerotic osteogenic sarcoma arising in the lower end of the femur in a 1 year old girl. This tumor is fan shaped with radiating spicules of new bone. Periosteal reaction has extended up along the shaft and the already ossified epiphyseal line has been invaded. (See Plate IX Fig 1 for gross specimen.)

A multiple myeloma usually presents many areas of punched out bone destruction with little periosteal reaction and thinning of the cortex of bone (Fig 704). These lesions are most prominent in the pelvis, skull, ribs, vertebrae, sternum, and clavicle. If multiple myeloma is suspected, roentgenograms of all these regions should be taken. In certain rare instances the involvement of these bones may be diffuse suggesting osteoporosis. Rib fractures are commonly seen. The solitary myeloma may be perplexing because at times it presents





Fig. 692—Rapidly growing of humerus in a 15-year-old boy. The mentation of the periosteum and the intact

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shaft with  
epiphysis

A roentgenogram of an *ameloblastoma* reveals a tumor involving the subperiosteal and cortical portions of the tibia. There is usually considerable involvement of the medullary cavity and the tumor may extend out into the soft parts. The epiphysis is not invaded.

**Laboratory Examination**—The laboratory examinations are of more value in *multiple myeloma* than in any other bone tumor. If the disease has become disseminated, plasma cells are only rarely found in the circulating blood stream. Bence Jones proteinuria is found in about two thirds of the cases, but it may be present in one specimen and absent in another. Bence Jones proteinuria, however, is not diagnostic, for it can also occur with metastatic neoplasms or with leucemias. Hyperproteinemia, because of elevation of the globulin, is a common finding in the advanced cases. In thirty cases of multiple myeloma reviewed by Gutman fourteen of the patients showed a serum protein higher than 9 Gm per 100 cc, and ten showed a value as high as 12 Gm. Occasionally the uric acid is prominently elevated. Hypercalcemia is frequent, Gutman's twenty one patients had calcium of 15 mg. per 100 cc or higher.

In *Ewing's sarcoma* the leucocyte count is often elevated from 10,000 to 15,000; the sedimentation rate is also constantly elevated and it may be the first sign of recurrence of the tumor.

The alkaline phosphatase is not a diagnostic test in bone tumors for it only reflects bone production. It is therefore elevated in the sclerosing forms of osteogenic sarcomas and normal in the osteolytic varieties. Alkaline phosphatase may also be elevated in Paget's disease and osteoblastic metastatic carcinoma.

**Biopsy**—Incisional biopsy of bone tumors is often considered dangerous inasmuch as some authorities believe that it may cause infection or spread of the tumor. This danger is overemphasized; however, the Coleys reported that twenty seven of their thirty five patients cured of sarcoma of the long bones had a previous incisional biopsy without infection or evidence of spread. Incisional biopsy may readily be done if the tumor has ulcerated the skin but this rarely happens. In tumors which have not ulcerated the skin, aspiration biopsy may be successful in obtaining tumor tissue when the neoplasm has extended into the soft tissue or has destroyed the periosteum. In certain instances the diagnosis by aspiration biopsy may be difficult (see chapter on pathology). If aspiration biopsy is inconclusive a frozen section may be diagnostic at the time of operation. If there is still any doubt of the diagnosis an incisional biopsy should be performed and permanent sections awaited.

Infection confuses the diagnosis of a bone neoplasm. It should be emphasized that no diagnosis should be attempted on a poorly prepared slide and that it may be necessary to take several biopsies before a representative area is obtained. If plasma cell myeloma is strongly suspected aspiration or bone marrow biopsy of the sternum is often diagnostic.

**Differential Diagnosis**—Most of the confusion that has existed regarding the giant cell tumor has been due to the fact that there are numerous other lesions which crudely caricature it. It is imperative that the giant cell tumor be identified and isolated from this group, for its pathologic behavior and clinical evolution are distinctive.

The most common lesion misinterpreted as a giant-cell tumor is the *bone cyst*. Table LXIV enumerates the differences between these two lesions. The

TABLE LXIII DIFFERENTIAL CHARACTERISTICS OF THE FOUR MOST COMMON MALIGNANT BONE TUMORS

	GIANT CELL TUMOR	EWING'S SARCOMA	OSTEOGENIC SARCOMA	MULTIPLE MYELOMA
Sex	Females predominate	Males predominate	Males predominate	Males predominate
Age (highest incidence)	20 to 35	1 to 20	10 to 30	Usually over 40
Location in bone	Epiphysis	Shaft	Metaphysis	Shaft
Most common sites	Lower end of femur, upper end of tibia, lower end of radius, maxilla	Femur, tibia, humerus, mandible	Lower end of femur, upper end of tibia, upper end of humerus	Bones of pelvis and femur
Metastases	Practically never	Lymph nodes, lung, skull, ribs, vertebrae	Lungs, practically never in lymph nodes	Skull, ribs, vertebrae, practically never lungs
Most important differential diagnosis	Bone cyst	Osteomyelitis	Bone cyst, metastatic carcinoma	Metastatic carcinoma

TABLE LXIV DIFFERENTIAL CHARACTERISTICS OF BONE CYSTS AND GIANT CELL TUMORS

	SOLITARY BONE CYST	GIANT CELL TUMOR
Age of greatest frequency	5 to 15 (under 20)	20 to 35 (over 20)
Sex	M > F	F > M
Site of origin	Metaphyseal	Epiphyseal
Bones of election	Humerus (Upper end) Tibia (Upper end)	Femur (Lower end) Tibia (Upper end) Radius (Lower end)
Clinical course	Fracture (Common) with spontaneous healing	Fracture (Uncommon), no spontaneous healing

bone cyst occurs predominantly in patients under 20 years of age, is more frequent in males, and occurs in the metaphyseal region. Fracture following minor trauma is common and occurs invariably in the proximal portion of the cystic area (Jaffe, 1942). Fifty per cent of the bone cysts occur in the upper portion of the humeral shaft. The giant-cell tumor occurs as a rule in patients over 20 years, is more common in females, and is found in the epiphyseal region. Both of these lesions have sites of predilection. The differential diagnosis between a single bone cyst and osteolytic osteogenic sarcoma may be very difficult because the patients may be in the same age group (below 20 years), the lesion is in the metaphysis, and fractures also occur in both. The osteogenic sarcoma is asymmetrical and the bone cyst symmetrical. There is no periosteal reaction in the bone cyst, but it may be present in the osteogenic sarcoma. Very few constitutional reactions are present in the bone cyst in contrast to fever, pain, increased local temperature, and skin changes in the osteogenic sarcoma. *Osteitis fibrosa cystica* shows multiple lesions which occasionally may be confused with giant-cell tumors. These cystic lesions, like single bone cysts, do not involve



Fig. 693.—Gross specimen of the same telegenic sarcoma with fan shaped appearance of the tumor, extension down the shaft, well-defined periosteal cuffing, and areas of hemorrhage within the tumor.

and biopsies may not be deep enough to reveal tumor. When the tumor is incised because it is thought to be an inflammatory process, milky material erroneously thought to be pus exudes from it. The Garré type of sclerosing osteomyelitis mimics a Ewing's sarcoma in some respects, but it is sudden in onset and it rapidly becomes chronic, while Ewing's sarcoma is mild in onset and becomes acute. In acute osteomyelitis the temperature is often high, the white count is excessively elevated, and a primary focus of infection is present. Often no bone lesion is seen. In chronic osteomyelitis an involucrum is often present, and this is never seen in Ewing's sarcoma.

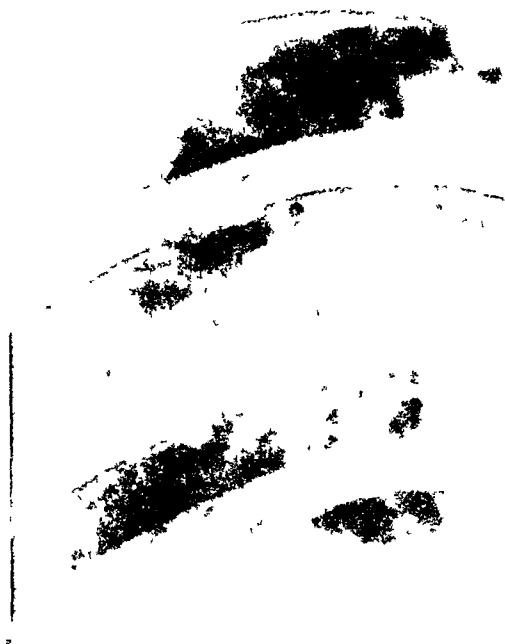


Fig. 696—Osteochondromatous lesion of the rib simulating osteogenic sarcoma in a 28 year-old man. The changes suggest that the tumor was not well circumscribed but at operation it proved to be well delineated. This patient has been well for four years. (See Plate IX Fig. 5 for gross specimen.)

*Bone tuberculosis* may be considered in the differential diagnosis of bone tumors but usually roentgenograms of the chest reveal evidence of healed pulmonary tuberculosis. Aspiration of any fluid with guinea pig inoculation is also diagnostic. In tuberculosis, the upper portions of the bone show destruction of the epiphysis, involvement of the joint cavity, and calcification of the soft parts. Infection plus tuberculosis is harder to diagnose because the excessive new bone production simulates the sclerosing type of osteogenic sarcoma.

the epiphysis but are associated with striking alterations of blood chemistry and are coexistent with a parathyroid adenoma (Albright). Benign *chondroblastoma* of bone is a very rare tumor which once was designated as an epiphyseal chondromatous giant cell tumor (Codman 1931). These tumors usually begin before the age of 20, occur more frequently in males and, because they begin in the epiphysis and present giant cells on microscopic examination, may be confused with giant cell tumors (Jaffe). However, on microscopic examination, calcification and small areas of focal necrosis are always present. *Fibrous dysplasia* of bone and *nonosteogenic fibroma* of bone are also mistaken for giant cell tumors mostly because they show the presence of giant cells (Jaffe).

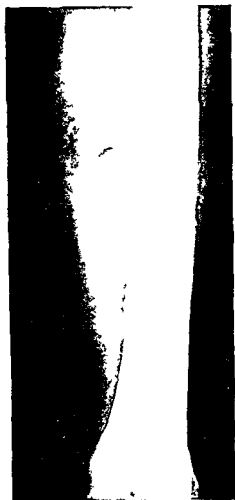


Fig 694

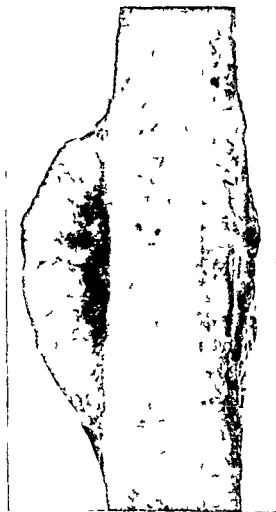


Fig 695

Fig 694—Osteogenic sarcoma of the shaft of the femur in a 66 year old male. The soft tissue mass extends out from the shaft of the bone and contains formation of new bone and alteration of the normal markings of the cortical bone.

Fig 695—Gross specimen of the same lesion showing tumor extensively involving the marrow cavity and extending to form a soft tissue mass.

The most frequent erroneous diagnosis made in a patient with Ewing's sarcoma is *osteomyelitis*. This can be easily understood because intermittent pain may follow trauma and is usually accompanied by constitutional reactions

The rapidly growing osteolytic type of osteogenic sarcoma may produce changes suggesting Ewing's tumor but it does not involve the shaft except in advanced cases

Metastatic *neuroblastoma of the suprarenal gland* is impossible to differentiate from Ewing's sarcoma from the bone changes alone (Barden), but neuroblastoma occurs predominantly in early childhood and roentgenograms of the abdomen and intravenous pyelograms may reveal evidence of a tumor in the region of the suprarenal gland. The biopsy of metastatic lymph nodes seldom helps in the differential diagnosis because the rosettes of a neuroblastoma are frequently absent. There is no doubt that a few cases of metastatic neuroblastoma are diagnosed as Ewing's sarcoma and their true nature revealed only when post-mortem examination is done (Willis)



Fig 699

Fig 700

Fig 699—Large soft tissue tumefaction caused by a chondrosarcoma of the upper end of the femur

Fig 700—Roentgenogram of the same lesion illustrating a central chondrosarcoma which has caused a fracture and the formation of a large soft tissue mass. There has been extension down the shaft of the bone. (From Sugarbaker E. D. and Ackerman L. V. Surg Gynec & Obst. 1945) (See Plate IX, Fig 3 for gross specimen.)

The sclerosing form of *syphilis of bones* can strikingly resemble sclerosing osteogenic sarcoma (Westermarck). However, the syphilitic bone changes are often symmetrical. There are two processes usually present: a destructive gummatous necrosis usually multilocular and a bone-producing, usually periosteal, formation (Fig 707). The gummatous necrosis manifests itself mainly in the periosteum and the cortex of the bone, resulting in small, well defined



Fig. 697—Osteogenic sarcoma of the skull superimposed on Paget's disease. (Specimen contributed by Dr. Robert A. Moore, Department of Pathology, Washington University School of Medicine, St. Louis, Mo.)

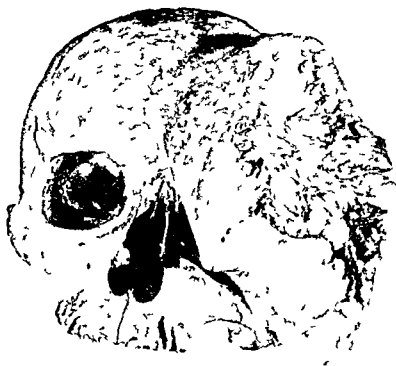


Fig. 698—Gross specimen of the same bone-producing lesion. (From Moore, Robert A., A Textbook of Pathology, Philadelphia, 1944, W. B. Saunders Co.)



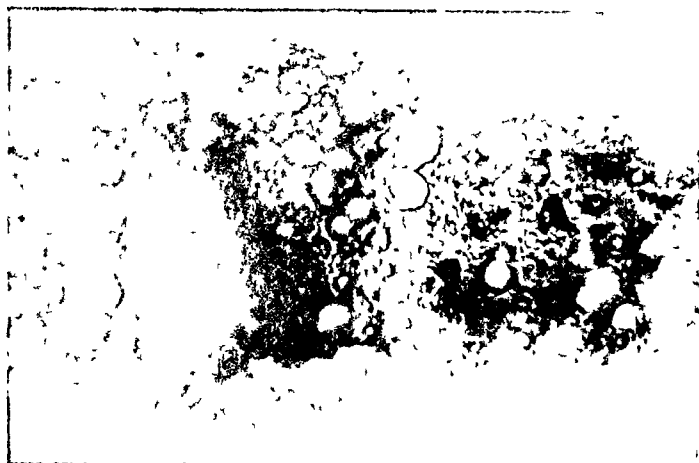


Fig. 16—Actinic keratosis of the skin showing multiple areas of epidermal repair at the borders and center



Fig. 17—Actinic keratosis of the pubic skin following roentgentherapy for carcinoma of the cervix

defects often surrounded by sclerotic bone. These changes usually develop in the flat bones of the hands and feet but they can also be localized in the diaphysis of the long tubular bones. The necrotic and sclerotic processes are most often equally apparent, but once in a while, one may predominate. This combination of destructive changes with clearly defined osteosclerosis is characteristic of syphilis. Antisyphilitic therapy usually results in fairly rapid healing of the defects. A positive serology and a careful history are also helpful in the diagnosis. *Metastatic carcinoma* may also be confused with osteogenic sarcoma, but it usually occurs after 40 years of age, does not affect the contour of the bone, and in the long bones develops in the region of the nutrient artery (humerus, femur, tibia). It can at times, almost exactly mimic osteogenic sarcoma (Figs 709 and 710), MacDonald has observed this in tumors arising from prostate, stomach, ovary, lung, and breast.

*Myositis ossificans* may present histologic findings difficult to differentiate from osteogenic sarcoma but the clinical and radiologic evidence usually yields sufficient information to resolve the diagnosis between the benign and malignant process.

The *enchondroma* must be differentiated from the chondrosarcoma but it is a benign cartilaginous growth appearing mainly in the phalanges of the metacarpal bones, femur, and humerus. In the small bones it produces an area of rarefaction with thinning and bulging of the cortex. In the long bones it appears in the region of the metaphysis and probably arises from islands of cartilage cells derived from the epiphyseal cartilage. In Jaffe's twenty-eight cases (1913) thirteen occurred in the finger phalanx, five in the metacarpal bone, five in the humerus, three in the femur, one in a toe phalanx, and one in a metatarsal bone. The enchondromas arising in terminal phalanges practically never become chondrosarcomas.

In the single focus myeloma the diagnosis may be very difficult. A single osteolytic punched-out area in a bone can be exactly reproduced by an *osteolytic metastasis* from some obscure primary source (the trabeculated cystic type can suggest giant cell tumor). In these instances the diagnosis can be resolved only by biopsy. An *eosinophilic granuloma* of the bone can also cause punched-out areas but this lesion usually occurs before puberty, in Green's series the patients ranged between 1 and 10 years of age. This disease is merely a phase in the development of Hand-Schüller-Christian disease. Biopsy is diagnostic. Clinically multiple myeloma can be confused with Paget's disease because of the thoracic deformities. However, in Paget's disease the alkaline phosphatase is elevated and in multiple myeloma it is normal. Paget's disease is characterized by other phenomena such as bowing of the legs and increased size of the skull.

### Treatment

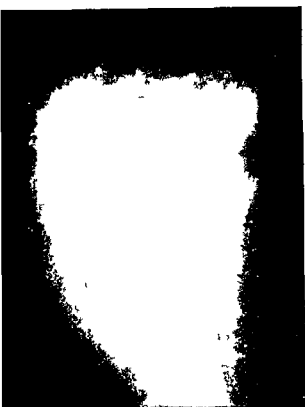
**SURGERY**—Surgical resection of *giant cell tumors* may be done when the resection does not imply impairment of function (involvement of ulnar ribs, metatarsal bones, patella and fibula). Also a radical surgical resection of giant cell tumors may be indicated when biopsy shows evidence of malignancy.

or when radiotherapy has previously failed. When a resection implies impairment of function, a thorough curettage followed by cauterization with zinc chloride is advocated by some surgeons. Filling the cavity with bone fragments in order to fill the defect is not recommended. A certain proportion of cases treated by curettage recur, and for this reason we feel that it is preferable to treat giant-cell tumors by roentgentherapy when they are located in the long bones and when resection implies major dysfunction.



Fig. 701—Roentgenogram of a peripheral type of chondrosarcoma arising from the cartilaginous cap of a pre-existing cartilaginous exostosis in a 21-year-old girl.

It is questionable whether the surgical treatment of *Ewing's sarcoma* should ever be undertaken. However, it is generally accepted that if the tumor is found in a patient over 15 years of age and is localized to a single bone, an amputation is indicated. Radiotherapy, however, can sterilize locally any such lesion, its failure is usually due to the presence of distant metastases.



A



B

Fig 702—A Advanced chondrosarcoma with blotchy areas due to irregular deposition of bone (From Sugarbaker L D and Ackerman L V Surg Gynec & Obst. 1945)

B Clinical photograph showing huge tumor with still intact skin. The patient remains well more than three years after disarticulation of the innominate bone.



Fig 703—Surgical specimen of the same lesion revealing the cartilaginous framework with numerous cystic spaces

The only successful treatment of *osteogenic sarcomas* and *chondrosarcomas* is radical surgical resection. An amputation above the proximal joint of the affected bone is accepted generally as the procedure of choice. This treatment applies in all instances except when the tumor is located in the distal end of the femur, in this instance an amputation at the level of the femoral neck is usually done. If the tumor is located in the upper portion of the humerus, an interseapulothoracic disarticulation is favored (Pack). Osteogenic sarcomas and chondrosarcomas of the pelvic bones and head of the femur may be successfully treated by disarticulation of the innominate bone (Sugarbaker), but this radical procedure is only justified in special instances. Conservative treatment such as surgical excision and repair with bone graft is only justified in a very few carefully selected cases of sclerosing osteogenic sarcoma or well-differentiated chondrosarcoma (Phemister). Single focus *myelomas* occurring in resectable locations (clavicle, rib, or humerus) may be treated surgically with a fair chance of success (Cutler). Surgery is not justified, however, when there are multiple lesions or when tumor is growing in the flat bones of the skull.

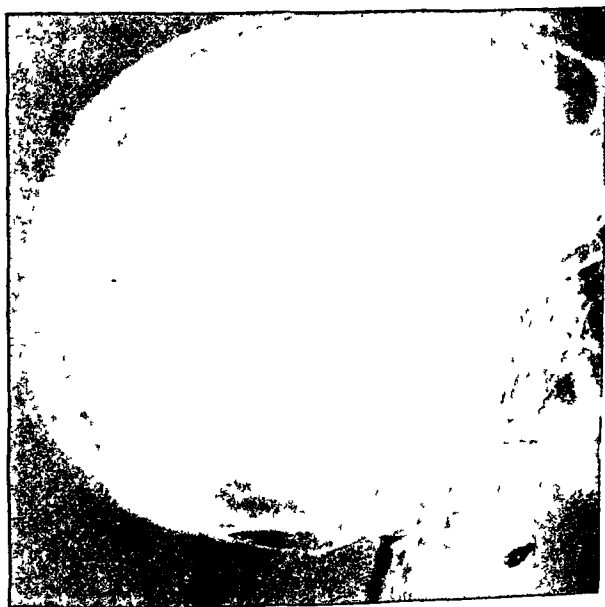


Fig. 704—Roentgenogram of multiple myeloma diffusely involving the skull and presenting typical punched-out areas of osteolytic destruction.

*Liposarcomas* and *hemangioendotheliomas* of the bone should be treated by radical surgery. *Ameloblastomas* may be treated by a conservative resection but not by curettage. If the ameloblastoma is advanced when first seen, an amputation should be done. Parker feels that the best treatment of *reticulum cell sarcoma* is a radical operation, but this lesion is also very radio-sensitive.

**RADIOTHERAPY** —The majority of benign *giant cell tumors* are radiocurable, and for this reason roentgentherapy should be used in preference to surgical excision. Pfahler first successfully treated a giant cell tumor by irradiation. That radiotherapy is the treatment of choice of these tumors is well substantiated by serious work which has been sporadically published in the last few years.



FIG 705

Fig 705.—The Garré type of chronic osteomyelitis

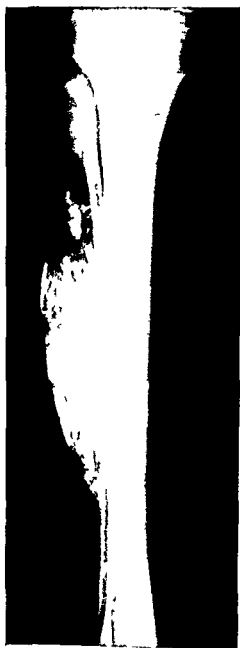


FIG 706

Fig 706.—Partially calcified hematoma suggesting Ewing's sarcoma

(Pfahler, Lacharité, Leucutia, Gershon-Cohen, Baclesse, Jansson) Roentgen-therapy does not need to be very forcible, and total doses may be kept well below those necessary for sterilizing malignant tumors. Consequently, untoward effects are not to be feared. The response of the tumor to radiotherapy is very slow and may continue for a period of years following a short series of treatments. The response to treatment consists of a slow reduction in the size of the tumor with progressive recalcification (Fig 712). At times the recalcification may be interrupted by osteolytic thrusts. These thrusts do not necessarily represent

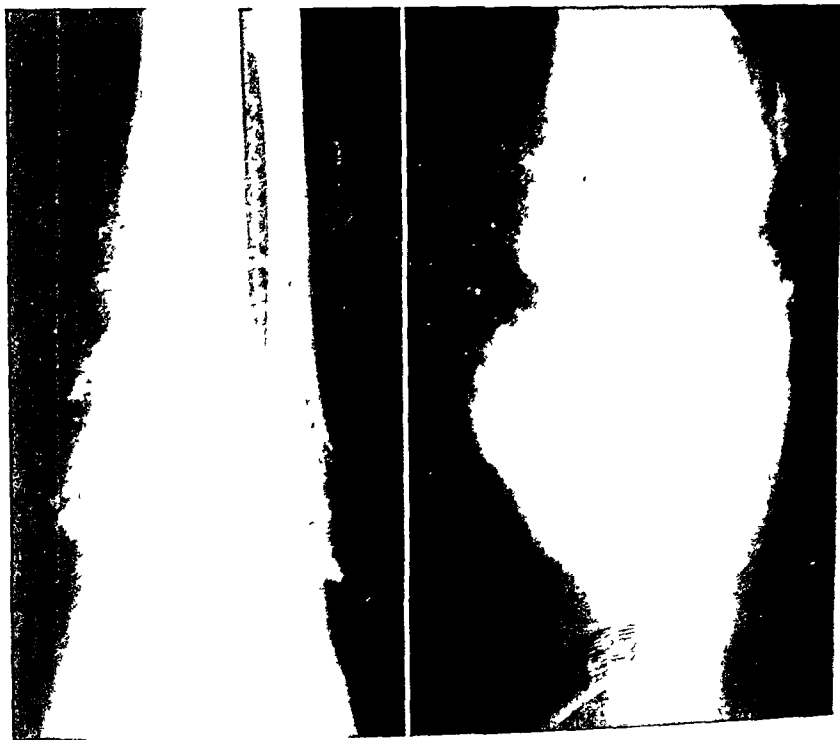


Fig 707

Fig 708

Fig 707.—Bone formation at right angles to the shaft in syphilis of the lower end of the tibia. These changes resolved following antisyphilitic therapy.

Fig 708.—Syphilitic lesion of the upper end of the tibia with bone destruction and bone production. This tumor was first erroneously considered an osteogenic sarcoma. (Courtesy of Dr Murray Stone, Springfield, Mo.)

malignant transformation and are typical of this type of tumor. Repeated series of radiation therapy may be necessary after long intervals. In a few instances radiotherapy may fail, but if the treatments have been protracted and the total dose have been low, the changes will not interfere with surgery.

Radiotherapy is the treatment of choice for a *Ewing's sarcoma*, for it is an extremely radiosensitive tumor capable of being cured locally. Subjective im-

provement follows the first treatments, and, in addition, roentgentherapy may avoid compression of the spine and the development of paraplegia when the tumor develops in vertebrae. The tumor regresses rapidly and becomes densely calcified. Failure of treatment is most often due to the appearance of other bone lesions or pulmonary metastasis.

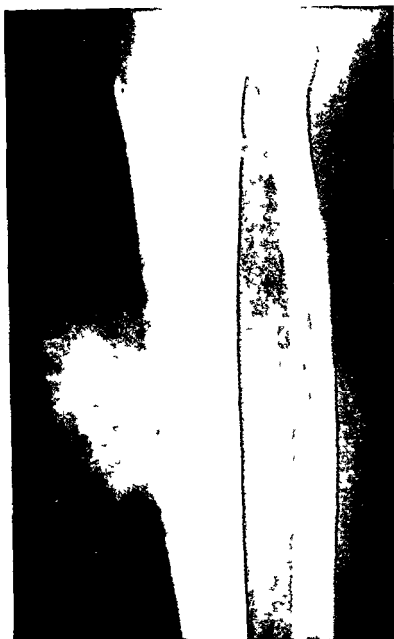


Fig. 99.—Bone producing lesion in the tibia suggesting an osteogenic sarcoma but actually due to metastatic adenocarcinoma. The primary lesion was located in the sigmoid.

*Myelomas* are very radiosensitive and locally radiocurable. Conservative treatment of multiple new lesions increases life expectancy. In the single focus myeloma radiotherapy may sometimes permanently control the disease. In order to attain total local sterilization treatment should be continued even after





THE FOLLOWING INFORMATION IS FOR THE USE OF THE





Fig. 711B—Characteristic osteolytic defect in the metaphyseal end of the humerus due to metastatic carcinoma arising from the breast. The lesion was treated by roentgentherapy became partially recalcified, and symptoms of pain were alleviated. (Courtesy of Dr. Alfonso Frangella, Institute of Radiology of the Faculty of Medicine, Montevideo, Uruguay.)



Fig. 1—Clavicle tumor before and ten years after radiotherapy. (From Leucutia, T.; Radiology 1941.)



Fig 710 —Characteristic osteolytic metastasis of the innominate bone. The primary tumor was an adenocarcinoma of the kidney



Fig 711A —Metastatic Ewing's sarcoma of the malar bone suggesting a primary osteogenic sarcoma. Note prominent spiculation

larger dose may result in bleeding from the dermis followed by secondary infection and loss of substance, which is known as *acute radiodermatitis*, a true radionecrosis of the dermis which is not reparable unless it is very limited.

The *permanent sequelae* resulting from irradiation of the skin are also varied. With a small dose the epilation produced is only transitory, but when a radioepidermitis has been produced, the epilation is usually permanent. Except for epilation there may be little visible sequelae even after a radioepidermitis, but achromia, fibrosis, atrophy, and telangiectasis may gradually develop in very variable degrees (Fig 18), depending on intensity, the region, idiosyncrasy, etc. An intense radioepidermitis with long period of repair may give place to a discolored atrophic skin which becomes dryer and less pliable (Fig 19) and may easily break down years later (spontaneously or following trauma and secondary infection), the result is a necrotic ulceration, a *late radiodermatitis*, the development of which may be due as much to a lack of local vitality as it is to trauma and infection.

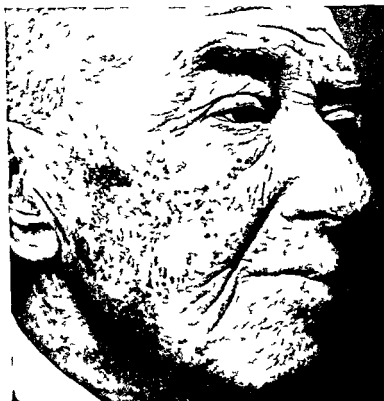


Fig 18—Slight achromia and atrophy of the skin of the face several years after roentgen therapy for a carcinoma of the superior maxilla.

The radiobiologic mechanism of skin reactions is one of the best examples of selective cytotoxic effect of radiations. Beyond a certain minimum dose the administration of a single dose of radiations may destroy the life of the cells of the germinal layer of the epidermis and hair follicles, all or most of which die immediately or shortly afterward in abortive mitoses. The irradiation has very little if any effect on the more superficial cells of the epidermis; the hair stops

the clinical disappearance of the tumor, for most failures may be laid to an insufficient total dose

Radiotherapy has no place in the treatment of *osteogenic sarcomas* because these tumors do not respond to this form of treatment. Radiotherapy combined with surgery is of questionable value. In tumors of such gravity, no delay in the radical surgical treatment would be justified.

### Prognosis

The prognosis of *giant-cell tumors* is excellent. Pfahler, Lacharrité, Leucutia, Baclesse, Geishon-Cohen, and Jansson, among many other authors, have reported numerous instances of permanent control of these tumors following irradiation. Wide surgical excision may be equally successful. Curettage of the bone followed by zinc chloride cauterization is followed by recurrence in about one-fourth of the cases. Inadequate radiotherapy may also result in recurrences.

*Ewing's sarcoma* has an extremely poor prognosis. The Bone Tumor Registry collected fifty-five cases which had been followed five years or more, and there were fifteen five-year survivals. Nine of the patients were treated by a combination of radiation therapy and surgery, five by surgical resection, and one by roentgentherapy alone (Phemister). It should be understood that this is a highly selected group of cases. Of 114 patients seen at the Mayo Clinic twenty-one lived five or more years. Of these, eight had amputations, two had wide excisions, and eleven were treated by radiations (Meyerding). Other reported series of treated cases have not shown such a high percentage results. Geschlechter reported 135 cases with only 6 per cent five-year survivals.

The prognosis of *osteogenic sarcoma* is related to many factors, and only when the majority of these are known can a prediction of the end results be made. The case with a long clinical history and a well-localized large tumor has a much better prognosis than the case with a very short history and a rapidly growing tumor. The osteolytic osteogenic sarcoma grows so fast and metastasizes so early that it has no time to attain any considerable size. Patients under 20 or over 50 years of age do much poorer than those between 20 and 40 years. The patients over 50 years have a poor prognosis probably because of the relatively high incidence of associated Paget's disease. In fact, if osteogenic sarcoma is superimposed upon Paget's disease, then the prognosis is very poor.

The type of operation may influence the prognosis. Conservative surgery performed for a rapidly growing tumor offers practically no hope of cure. If the tumor is not resected above the involved joint then tumor may be left to grow within the remaining segment of bone marrow. The location of the tumor is also important, for if it develops in an area where it cannot be surgically removed (skull, vertebra, and some pelvic bones), the condition is hopeless. Generally speaking, the nearer the tumor is to the trunk the worse is the prognosis. Osteogenic sarcomas of the scapula, clavicle, and middle and upper third of the femur have a poor prognosis. Conversely, osteogenic sarcomas arising from the small bones of the feet or forearm have a better than 50 per cent five year survival after surgical treatment.

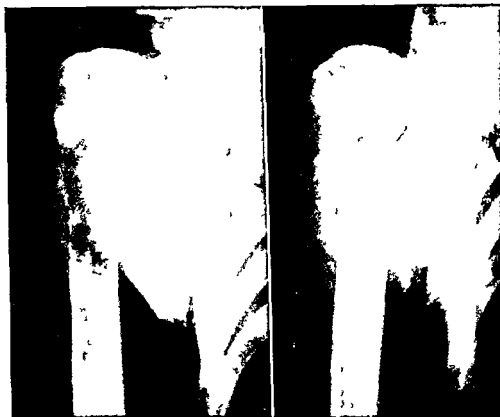


Fig. 11B—Characteristic lytic defect in the metaphyseal end of the humerus due to metastatic carcinoma arising from the breast. The lesion was treated by roentgentherapy, became partially recalcified, and symptoms of pain were alleviated. (Courtesy of Dr. Alfonso Frangella, Institute of Radiology of the Faculty of Medicine, Montevideo, Uruguay.)



Fig. 11A—Giant-cell tumor before and ten years after radiotherapy. (From Leucutia, *T. Radiology* 1941.)

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The pathology of a bone tumor is very significant in regard to prognosis. The well differentiated osteogenic sarcomas particularly those made up predominantly of adult fibrous tissue and cartilage, do very much better than the very undifferentiated rapidly growing osteolytic type of tumor. The osteolytic osteogenic sarcoma has an exceedingly poor prognosis. Of 131 cases reported by McReynolds from the Johns Hopkins University Hospital, only eleven of the patients survived more than five years. The average duration of life of patients who died within five years after treatment was ten months. In twenty eight cases of surgically treated osteogenic sarcomas reported by Simmons eleven of the patients lived five years or more after operation, a high percentage of these sarcomas were well differentiated. MacDonald studied 118 five year survivals from the Bone Tumor Registry and reported essentially the same differentiated type of pathology predominating in these cases as in those of Simmons. He found that among the cured cases there were fourteen osteosarcomas, fifty six chondrosarcomas and thirty seven fibrosarcomas. In a large unselected group of 100 cases (only sixty histologically proved) Coley and Pool reported thirty five five year survivals. They divided their cases into low, average, and high grade malignancy. Forty three per cent of the five year survivals were in the low grade group, 46 per cent in the average, and only 11 per cent in the high grade. Chondrosarcomas have a much better prognosis as a group than osteogenic sarcomas (MacDonald, Simmons, Jaffe). It is probable that the chondrosarcomas arising peripherally from exostoses have a better prognosis than the central chondrosarcoma.

If the *myelomas* occur first as a single focus in the bone and are treated locally then a fair percentage of the patients have a five year survival (Cutler). Other myelomas become generalized and assume the typical form of a multiple myeloma. After generalization, the life expectancy is not longer than two years. Jackson reported on six patients with reticulum-cell sarcoma of bone treated by amputation followed by postoperative irradiation. One of these died at the end of two years and five were living between six and sixteen years.

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## Chapter XVII

### SARCOMAS OF THE SOFT TISSUES

Soft tissue sarcomas are a small and exclusive group of tumors of mesodermal origin (smooth muscle, striated muscle, fat, connective tissue, and blood vessels). Their frequency is illustrated by Table LXV, which demonstrates

TABLE LXV PRIMARY SARCOMAS OF THE SOFT PARTS JULY, 1906—JULY, 1916, INCLUSIVE  
(From Stout, A. P. I. Missouri M. A., 1917)

TUMOR	TOTAL CASES	FOLLOWED CASES	INCIDENCE	METASTASIS	DIED TUMOR
Fibrosarcoma	181	120	66 (56)	9 (8)	15 (14)
Liposarcoma	73	35	23 (66)	12 (34)	13 (37)
Rhabdomyosarcoma	25	20	17 (85)	8 (40)	13 (65)
Leiomyosarcoma	13	10	9 (90)	3 (30)	8 (80)
Hemangioendothelioma	12*	7	6 (86)	5 (71)	3 (43)
Hemangiopericytoma	25*	12	5 (42)	2 (17)	3 (27)
Synovial sarcoma	9	7	6 (86)	6 (86)	6 (86)
Mesenchymoma	6	5	2 (40)	3 (60)	3 (60)
Total	347	216	133 (62)	48 (22)	64 (30)

\* Excluding benign forms in infants.

Figures in parentheses represent percentages of followed cases.

The fibrosarcomas include dermatoids and the dermatofibro-sarcoma protuberans of Hoffman.

that fibrosarcoma and liposarcoma are the most frequent. They appear at any site where the parent tissue is present. Their rate of growth is unpredictable. Not included in this group are the lymphosarcomas and the sarcomas of special organs (for example leiomyosarcoma of the uterus). The soft tissue sarcomas of the mediastinum (which could be included in this group) are discussed in the chapter on tumors of the mediastinum.

Table LXVI tabulates the five most common types of soft tissue sarcomas in respect to the sex, incidence, mean age, common locations, origins, and gross and microscopic characteristics.

### Pathology

**Gross and Microscopic Pathology**—The pathology of the soft tissue sarcomas may be varied because of their mesodermal origin. However, differentiation of the specific types can usually be made because of the location of the tumor and its pathologic characteristics. Exact histogenesis may be determined with special stains and in a few instances by tissue culture (Murray). All of these tumors are capable of producing reticulum. A small group, however, may defy exact classification. (See chapter on pathology for information regarding proper fixation and staining.)

**Fibrosarcoma**—Fibrosarcomas arise most commonly from the thighs, upper extremities, and the flexor surface of the forearms. They can arise from the

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superficial subcutaneous connective tissue, deeper connective tissue, or periosteum. They may be multimodular in the skin and be designated as dermatofibrosarcoma protuberans (Hofmann). Stout believes that malignant tumors arising from nerve sheaths are frequently associated with von Recklinghausen's disease. He feels that the active cell in these tumors is neuroectodermal in

A



B

FIG. 713—A, Photomicrograph of a well-differentiated fibrosarcoma showing characteristic spindle-shaped cells (moderate enlargement).  
B, Photomicrograph of a moderately differentiated fibrosarcoma. Note numerous mitotic figures.

TABLE LXVI SUMMARIZED CHARACTERISTICS OF MOST COMMON VARIETIES OF SOFT TISSUE SARCOMAS

	FIBROSARCOMA NFIBROSARCOMA	LIPOSARCOMA	PHANOMIOSARCOMA	SYNOVIAL SARCOMA	HEMANGIOENDOTHELIOMA
Sex	No definite preponderance	No definite preponderance	Slight male preponderance	Males 3 to 2	Data insufficient
Mean age	30 (Warren and Sommer)	All ages	All ages	32 (Haugensen and Stout)	Data insufficient
Common locations	Extremities and trunk	Gluteal region, thighs and popliteal and retroperitoneal regions	Upper extremities and interscapular regions	About tendon sheaths and immediate vicinity of knee and ankle joints	Skin, subcutaneous tissue and muscle
Present tissue of origin	Connective tissue or nerve sheath	Adipose tissue	Striated muscle	Synovium	Blood vessels
Gross characteristics	Firm or soft, pseudocapsulated, grayish white	May be very large resembles brain tissue often pseudocapsulated	Rather soft pseudocapsulated, often hemorrhagic	1. Scudocircumscribed grayish pink hemorrhagic fibrous and calcified at times Two types of tissue forms present—one resembling synovial structures and the other suggesting fibrosarcoma	Very vascular, bleed within themselves or externally
Microscopic characteristics	Connective tissue cells of varying sizes, phosphotungstic acid hematoxylin demonstrates fibroglia and fibrils	Nucleus often compressed to eccentric shape by fat, cytoplasmic fat prominent with fat stains Sudan IV and carmalum are helpful in diagnosis	Gross striations infrequent best seen with phosphotungstic acid hematoxylin giant cells common, vacuolation of nuclei, transition from normal muscle at times seen	Silver stain demonstrates usually layering of endothelial tumor cells and anastomosing vascular channels	

Grossly, liposarcomas often show convolutions which crudely caricature cerebral cortex (Fig 715). In the depths of these convolutions there is a fine lacy network of blood vessels. On section, the tumor is usually a yellowish-white color, of somewhat slimy consistency, resembling brain tissue (Fig 715). Small satellite tumor nodules may be observed. Areas of necrosis, hemorrhage, and mucoid degeneration are common. Occasionally there may be multiple primary tumors (Ackerman).

The microscopic picture may be uniform or varied. The tumor can be well differentiated resembling embryonal fat, or it may have bizarre lipoblasts, some of them giant in size. Quite frequently the nucleus is compressed to a crescentic shape by the cytoplasmic fat (Fig 716). In other instances the lipoblasts have a central nucleus with very foamy, abundant lipid-containing cytoplasm. Tumors which merely show small areas of fatty degeneration should not be mistaken for liposarcomas. Specific stains for fat are particularly helpful in the diagnosis.

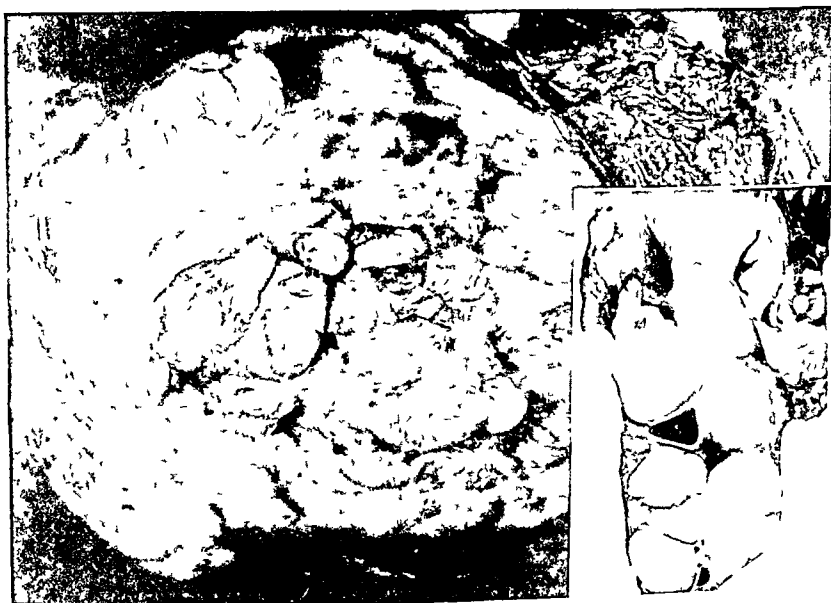


Fig 715—Gross specimen of a liposarcoma showing typical surface which caricatures cerebral convolutions. Insert represents a cross section of involved retroperitoneal lymph nodes. Note close resemblance to brain tissue.

*Rhabdomyosarcoma*—These tumors appear most frequently in the popliteal, gluteal, and interscapular regions. Abrikossoff was the first to divide the tumors of striated muscle into four groups, the first three invariably benign and the fourth malignant. The granular-cell myoblastomas belonging to the third group are rarely malignant. Crane recently collected 162 cases, the most common site of origin being the tongue. However, a malignant granular-cell myoblastoma arising from the urinary bladder (Ravich) and one arising from the gluteal

origin and therefore should be designated as a malignant schwannoma. The fact that a soft part sarcoma is perhaps intimately associated with a nerve does not necessarily mean that it is arising from its sheath. The malignant schwannoma has a striking tendency to recur locally and may be multiple. It is not infrequent for fibrosarcomas to infiltrate the skin fungate and ulcerate, and be the cause of hemorrhage. Grossly fibrosarcomas are firm and homogeneous, forming a rounded or spindle shaped mass which can become very large without infiltrating the surrounding structures. On section they are pale, grayish white in color and hemorrhage and necrosis appear with increasing frequency the larger the tumor. The tumors are made up of spindle shaped cells with a varied number of mitotic figures according to their differentiation (Fig 713). A silver stain reveals each individual cell to be wrapped in fibrils which also run parallel between the cells.



Fig 14—Fibrosarcoma of the thigh recurring after inadequate surgery. Note deep extension.

Warren attempted to separate the tumor of nerve sheath origin from the tumor arising from connective tissue in other locations. He believes the neurofibrosarcomas can be differentiated from fibrosarcomas because their cells are arranged in definite fascicles with an interlacing herringbone pattern and because the cells have a somewhat more elongated nuclei with some evidence of palisading of the nuclei. We have not been able to make such a differentiation. A differentiation can be more easily made by observing the association of the tumor with nerve sheaths and by finding stigmas of von Recklinghausen's disease (that is café au lait spots, subcutaneous nodules).

**Liposarcoma**—Liposarcomas occur in any area where fat is present (Fig 720). They are most commonly found in the popliteal space, the gluteal regions, the thigh, and retroperitoneal area. Sixty-four per cent of Stout's 73 cases arose in the thigh and retroperitoneal area. Infrequently they may arise from a pre-existing lipoma, but probably most liposarcomas are malignant from the start. They tend to grow very large.

growing and shortly afterward becomes detached from the matrix. Thus, while the normal desquamation of superficial epidermic cells proceeds, the constant supply of cells from the basal layer is stopped and, consequently, the epidermis becomes thinner each day, the intercellular spaces become enlarged (edema), and large amounts of polymorphonuclear leucocytes give the area a character of inflammation which justifies the name of epidermitis. Finally, the epidermis entirely disappears in about twenty-six to twenty-eight days. When this occurs, there may have been some reformation of new epidermis, so that dermis is

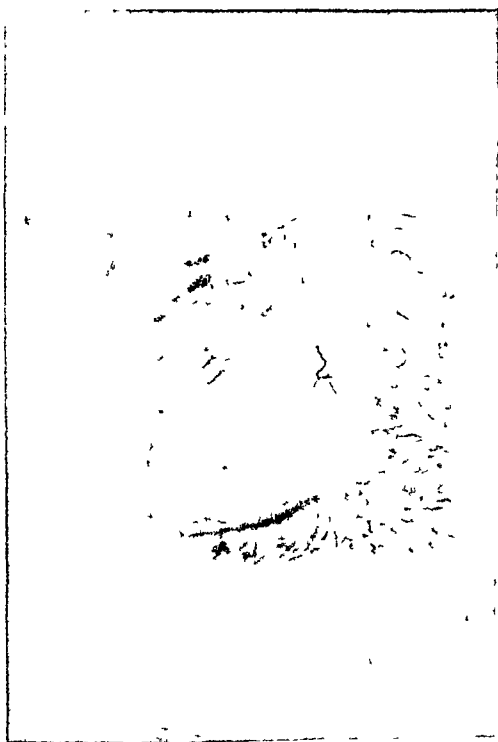


Fig 19—Atrophic changes with telangiectasias of the skin of the breast following intensive radiotherapy for an inoperable carcinoma

not actually denuded (dry epidermitis), but if the germinal cells have not yet started to repopulate the area, the papillae of the dermis lose their normal covering (moist epidermitis) until epidermal growth, from around the hair follicles and sweat glands or from the nonirradiated borders of the area, finally cover anew the dermis. At best, the new epidermis is thin, lacking in or with a scarcity of skin appendages, the papillae are flattened, the number of vessels present in the dermis diminishes with the increase of fibrosis, and, in compensation, some become dilated. In cases of acute or late radiodermitis there is loss

region (Ackerman) have been reported. In the fourth group are the relatively infrequent rhabdomyosarcomas. They often appear encapsulated and the gross transition from normal muscle to tumor may be seen. Areas of hemorrhage are prominent (Figs 717, A and 717, B). The microscopic examination reveals tumor growing in close proximity to or in intimate relation with striated muscle. Tennis racket shaped cells in particular may present cross striations or longitudinal myofibrils. Frequently, giant cells with peripherally arranged vacuolation (Fig 717, C) resemble spiders or spiderwebs (Stout). The cytoplasm is invariably strongly acidophilic, and nuclei may be arranged in a tandem.

*Synovial Sarcoma*—The synovial sarcoma occurs particularly around the knee, ankle joint, or near tendon sheaths. Approximately 80 per cent appear in the lower extremity (Haagensen) but the tumor only rarely involves the joint synovia. This is an important point in the differential diagnosis because synovial hyperplasia, hemangiomas and other benign lesions show involvement of the synovia.

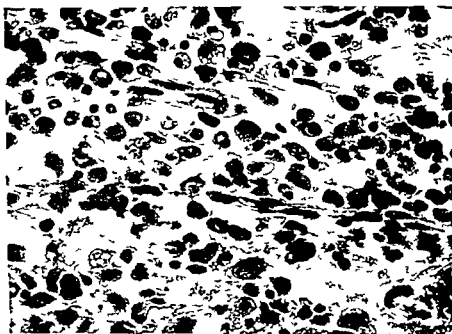
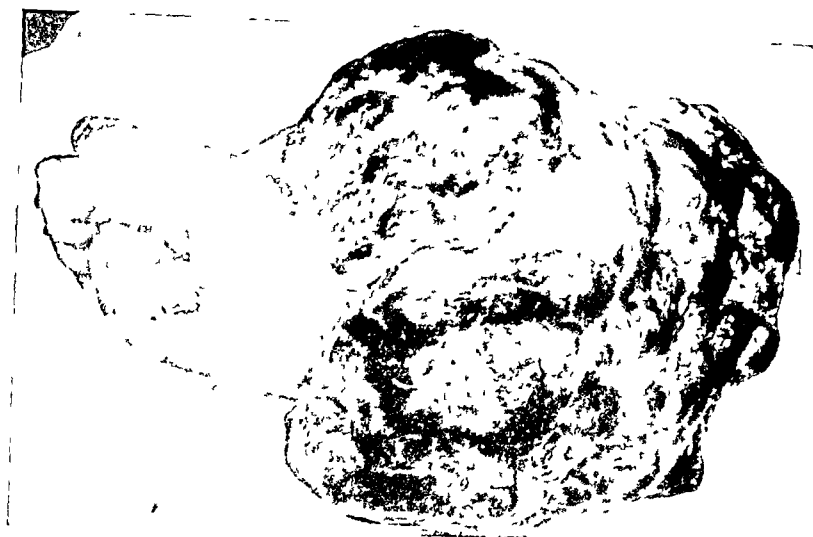


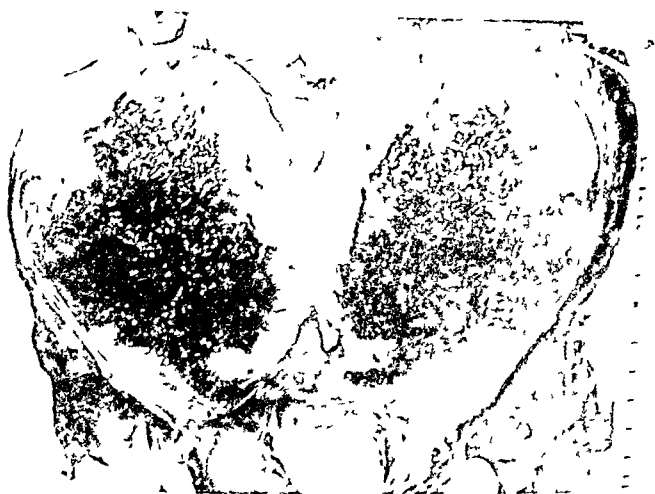
Fig 16—Photomicrograph of a liposarcoma. Note cytoplasmic vacuolation representing fat (moderate enlargement).

Grossly the synovial sarcoma is fairly firm, appears encapsulated and is grayish pink in color. On section it remains grayish pink but may show areas of hemorrhage and calcification. It is often firmly fixed to a neighboring structure (joint bursa, or tendon sheath). Microscopically there must be two elements present—an intimate intermingling web of adenomatous structures and a sarcomatous like stroma (Fig 718). These adenomatous areas may look very much like synovial membrane. The cells secrete a sticky mucoid substance hyaluronic acid which is usually found in joints. A single section may contain only one of these elements so that multiple sections should be studied in order to differentiate them from adenocarcinomas or fibrosarcomas.





A



B

Fig. 717—1. Clinical photograph of an ulcerating protruding large rhabdomyosarcoma of the foot. 2. Gross specimen of rhabdomyosarcoma with prominent areas of hemorrhage. 3. Photomicrograph of the same rhabdomyosarcoma. Note giant cell in the center with finger-like cytoplasmic process.

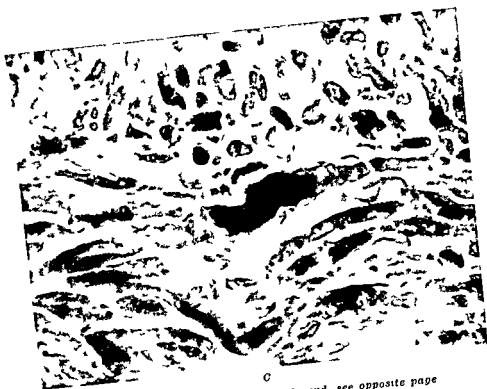


FIG 717 (Cont d) —For complete legend see opposite page



Fig 18 —Photomicrograph of a synovial sarcoma showing intermingling of adenomatous and sarcomatous like structures (moderate enlargement)

*Hemangioendothelioma*—The hemangioendothelioma is a malignant tumor of blood vessel origin and, although rare, may grow wherever there are blood vessels. It is most frequently seen in the subcutaneous tissues and muscle. The apparent encapsulation of the tumor is false. It tends to be very vascular so that if the tumor ruptures through the skin, then profuse bleeding may occur. The cut section is extremely hemorrhagic in appearance. The hemangiopericytoma and Kaposi's disease (questionably a neoplasm) also can be classified as malignant vascular tumors. The microscopic findings are characteristic (Fig 719), and silver stains clarify the picture by demonstrating a layering of the endothelial cells and the invariable presence of anastomosing vascular channels.

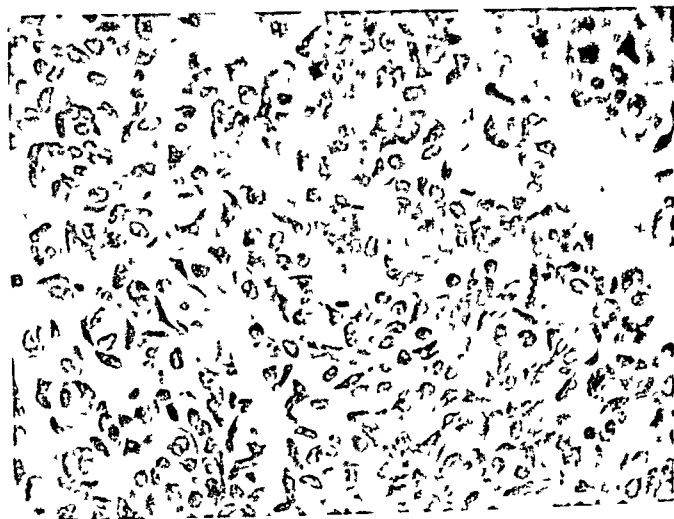


Fig 719—Photomicrograph of a hemangioendothelioma. Note suggestive blood vessel origin which was substantiated by silver stain.

*Osteogenic Sarcoma*—This tumor of the soft tissues is a most uncommon occurrence. It may be found within an area of myositis ossificans (Pack) or arising simply from metaplasia of connective to osteoid tissue (Ackerman). Grossly the tumor is firm and often presents interlacing-like nodules. The microscopic examination reveals osteoid tissue, and with a phosphatase stain by the Gomori method, the diagnosis is assured. The *leiomyosarcoma* is rare. Stout reported thirteen, of which nine were retroperitoneal. They resemble leiomyosarcomas elsewhere. Microscopically differential fiber stains may reveal myofibrils. Individual cells have blunt-ended nuclei. Stout has recently described the *mesenchymoma*, a tumor appearing as a soft part sarcoma but microscopically revealing an admixture of elements. These may contain all mesodermal elements, one area of the tumor resembling liposarcoma, another portion rhabdomyosarcoma, etc. To Stout this represents evidence of the versatility of the primitive mesenchymal cell.

*METASTATIC SPREAD*—All of these sarcomas tend to appear pseudoencapsulated, spread locally, and have a decided tendency to recur. They have certain

common characteristics in their metastases, which are very frequently carried by the blood stream. Regional lymph node metastases in *fibrosarcomas* occur rather frequently. In 280 cases reviewed by Taylor, fourteen had pathologically verified metastases to the regional nodes. The *synovial sarcoma* also metastasizes to regional nodes. In 104 collected cases, the inguinal nodes were involved in seven and axillary nodes in four (Hjagensen). *Rhabdomyosarcomas* and *liposarcomas* also involve regional lymph nodes but not nearly as frequently, and the extraosseous *osteogenic sarcomas* practically never have node metastases. *Leiomyosarcomas* often locally recur but infrequently have distant metastases. All of these sarcomas tend to metastasize distantly, particularly to the lungs and not infrequently to other organs such as liver and bone. Occasionally the metastases are widely disseminated to many organs.

### Clinical Evolution

Soft tissue sarcomas are discovered either by accident or because of symptoms due to their encroachment upon vital organs or nerves. Those arising in the soft tissues of the leg, thigh or upper extremity may reach a fairly large size before pain or disability occurs. In the retroperitoneal area and particularly around the kidney, the sarcomas may become huge before they provoke



Fig. 6.—Liposarcoma arising in the region of the anterior axillary fold. r—soft fairly well circumscribed and impossible to differentiate clinically from a lipoma. Patient remains well five years after radical excision.

symptoms by infringing upon the function of the neighboring organs (kidneys, ureters, bladder, or intestinal tract). If treatment is not instituted, they may burst through the skin to ulcerate and become infected. The rhabdomyosarcomas particularly tend to form reddish protruding masses. Hemorrhages from their surface with resultant secondary anemia and infection may cause general symptoms with fever and weight loss. Local pain is invariably present with advanced disease. With distant metastases, a rather profound weight loss may quickly ensue.

### Diagnosis

**Clinical Examination**—The diagnosis of the soft tissue sarcoma in most instances is quite simple. A knowledge of the characteristic locations of each type is useful. The consistency of the tumor depends upon the cellularity and connective tissue content. It may feel encapsulated by palpation. At examination, an attempt should be made to determine whether or not the tumor is attached to the overlying skin, muscle, or underlying bone, for this may determine operability. The retroperitoneal sarcoma is often very large at the time of the first examination and palpates as a rather large indefinite mass of variable consistency.

**Roentgenologic Examination**—The roentgenologic examination frequently shows the extent of the tumor, often seen as a somewhat circumscribed shadow with slightly increased density over the surrounding soft tissue. This examination is of greatest help in determining whether there is bone destruction or thinning of the cortex of the underlying bone due to pressure atrophy by the tumor. If periosteal thickening is present together with an irregularity of contour, it might suggest that the tumor is attached to the bone. Previous radiation therapy may confuse the roentgenologic appearance of the tumor. Pyelography and barium enema may be helpful by more accurately defining the location of a retroperitoneal tumor.

**Biopsy**—If the tumor has ulcerated through the skin, then incisional biopsy can be easily done. If the tumor lies deep, however, an aspiration biopsy is often successful in revealing sarcoma, but in many instances exact classification is not possible. Careful incisional biopsy may be necessary for exact classification which may, to some extent, modify treatment.

**Differential Diagnosis**—Soft tissue sarcomas may be confused with benign tumors such as lipomas, neurofibromas, hemangiomas, and leiomyomas. These benign tumors usually have a long clinical evolution with very slow increase in size. They are freely movable and not firmly attached to underlying structures. The sarcoma, on the other hand, ordinarily grows fairly rapidly and becomes fixed to the underlying tissue. A *sebaceous cyst* can become fastened to the overlying skin. In rare instances *Ewing's sarcoma* may have inconspicuous symptoms referable to bone and may masquerade as a soft tissue sarcoma. *Aneurysms* of large blood vessels can also be confused with a sarcoma, but the roentgenographic examination may help in differentiation. *Subcutaneous abscesses* are usually painful and are associated with fever and other signs of infection.

True fibrosarcomas should be carefully differentiated from *desmoid tumors* which occur most frequently in females, arise in muscular aponeurotic structures, and usually appear in the anterior abdominal wall. A very high percentage of

patients with desmoid tumors have an associated history of prolonged labor at childbirth. It is thought that trauma with resultant hemorrhage in the muscular aponeurotic structures may lead eventually to the production of a desmoid tumor. Other cases present a history of trauma or tumor in an operative scar. On gross examination desmoid tumors are well encapsulated, move beneath the intact overlying skin and may measure up to 10 cm in diameter. Microscopically they are composed of rather cellular connective tissue in striated muscle in contrast to the relatively acellular keloid (Pearman). They are best treated by wide excision, for if any of the tumor is left it may locally recur. They have never been known to metastasize.

*Metastatic carcinomas* growing in the soft tissue, particularly in the region of the knee joint or in the upper thigh can closely simulate a primary sarcoma. The diagnosis is most difficult when the primary tumor is asymptomatic. Carcinomas of the kidney are particularly inclined to produce this picture. Biopsy, pyelograms, roentgenograms of the chest, past history, and the clinical examination should resolve the diagnosis. The patient with a metastatic soft tissue tumor has often lost considerable weight and this is unusual with the well localized soft tissue sarcoma.

### Treatment

**SURGERY**—The treatment of soft tissue sarcomas is wide surgical excision. In the event that adequate margins of safety cannot be maintained by local excision of a sarcoma of the extremities, then amputation should be carried out. Generally amputation is not necessary in the well differentiated liposarcoma and skin fibrosarcoma. If the tumor is located in a region where an even more radical approach is indicated there should be no hesitation doing such a formidable procedure as disarticulation of the innominate bone or interscapulothoracic amputation (Sugarbaker Pack). The location of the tumor is therefore of great importance, for the prognosis may be dependent upon whether or not it is accessible to effectual surgical removal. It is unfortunate that all of these tumors show pseudoencapsulation for at exploration they may look benign and be treated by enucleation rather than by wide resection. Careful examination of the areas surrounding the pseudoencapsulation invariably reveals finger-like processes of tumor extending out into the surrounding soft tissue.

In the fibrosarcoma, neurofibrosarcoma, synovial sarcoma, and possibly, at times in the rhabdomyosarcoma, the question of carrying out a radical regional lymph node dissection may arise. If the regional nodes are enlarged and biopsy (incisional or aspiration) proves the presence of metastatic sarcoma a radical node dissection is indicated unless there is evidence of distant metastases.

**RADIOTHERAPY**—The liposarcoma is the only variety of sarcoma which is at all responsive to radiotherapy. The large bulky, inoperable liposarcomas may react to palliative roentgentherapy, but it probably can be used most effectively with a small local recurrence and as in adjunct to wide local excision.

### Prognosis

Because many of these tumors are treated conservatively the number of local recurrences is high (Fig 714, B). By the time the tumor recurs, distant metastases particularly in the lungs may be present.

In a series of 111 patients with *fibrosarcoma* reported on by Wilson, thirty-three (30 per cent) were reported clinically cured, thirty-two had been without disease from five to eleven years. There is a definite relation between the histologic character of the lesion and the prognosis (Table LXVII). The pres-

TABLE LXVII THREE YEAR SURVIVAL AFTER TREATMENT OF DIFFERENT VARIETIES OF FIBRO SARCOMA

(From Warren, S, and Sommer, G N J, Jr Arch Surg, 1936)

	NUMBER OF CASES	ALIVE AND WELL THREE YEARS	PERCENTAGE
Fibrosarcoma	13	15	35
Neurogenic fibrosarcoma	38	11	37
Fibrosarcoma with tumor giant cells	26	2	8
Neurogenic fibrosarcoma with tumor giant cells	11	1	36

ence of tumor giant cells is ominous (Warren). The prognosis is equally grave when there is marked variation in the size and shape of the cells and when mitotic figures abound. Meyerding followed 152 cases, twenty-eight of the patients living three years after operation and twenty-four surviving five to twenty years. The average duration of life was six years from the time the tumor was first noticed. On the whole, the more superficial tumors arising in the subcutaneous tissue have a better prognosis than do those in the deeper tissues which have a better opportunity to invade the blood vessels. The condition is usually hopeless when lymph node metastases have occurred. If a recurrence appears, it almost invariably occurs within the first year after surgery (Warren).

With a *liposarcoma*, the best prognosis may be conceded to the well differentiated superficial tumor for which radical excision has been done. The inaccessible or conservatively excised or undifferentiated liposarcomas do poorly. Haagensen collected 104 cases of *synovial sarcomas* in which the patients, for the most part, were treated conservatively. The ominous prognosis of this group was shown by the fact that only three were known to be free from metastases for more than five years after treatment. Stout collected 121 cases of *rhabdomyosarcoma*, 108 of the patients received treatment, and there were only four five-year survivals. There are no well-established statistics on the prognosis of the *hemangioendothelioma*.

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## Chapter XVIII

### CANCER OF THE EYE

#### Anatomy

Fig 721 is a sketch of a transverse section of the eye, and the different anatomic structures are labeled. A more detailed anatomical description is not necessary for our purposes.

**Lymphatics**—There are no lymphatic vessels in the lens or sclera of the eye, but lymphatic lacunae are found in the cornea, iris, and ciliary body. It is possible that the choroid possesses a system of lymphatic vessels. The lymph spaces of the retina communicate with those of the optic nerve. The palpebral lymphatics contain two networks, one superficial (cutaneous) and the other deep (conjunctiva). The superficial and deep collecting trunks of the lids communicate with each other and follow two pathways: one ends in parotid lymph nodes and the other in submaxillary lymph nodes (Rouxvière).

#### Incidence and Etiology

The *malignant melanoma* is the most common malignant tumor of the eye, although it makes up a relatively small proportion of all malignant melanomas. It appears most frequently in patients 50 to 70 years old.

*Retinoblastomas* occur in young children and have been reported in about one of every 34,000 births (approximately twenty cases per year) in the United States. These lesions occur in families. Weller reported thirty families in which this neoplasm occurred, at times in more than one-half of the children of one household. It may occur in successive generations or in collateral lines. The inheritance of predisposition to retinoblastoma can occur through both male and female. Some cases of retinoblastoma appear to be sporadic. Weller believes that there is a probable relation between the sporadic and familial groups and that a structural anomaly is inherited on the basis of which retinoblastoma may develop. *Lymphoid carcinomas* of the conjunctiva are very rare.

#### Pathology

**Gross and Microscopic Pathology**—The *malignant melanoma* arises most commonly in the choroid and ciliary body. In a few instances it arises from the conjunctiva and iris. The tumors originating in the iris may arise from pre-existing nevi. As the choroid melanoma increases in size, it displaces the basal lamella of the retina into the vitreous. The tumor may extend along the optic nerve. Eventually, it involves all the structures of the eye and, not too rarely, develops into an ulcerating fungating mass showing variable degrees of pigment (Figs 722 and 723). Numerous satellite nodules may surround the tumor.

of substance and infection of the dermis, the endarteritis which may then be observed is probably a consequence rather than the cause of this untoward effect

The effects of irradiation of the oral and pharyngeal *mucous membranes* are very similar to those observed on the skin except that, as it was pointed out by Coutard, the denudation of the dermis occurs in half the time, thirteen to fourteen days, and the dermis is rapidly covered with a diphtheroid membrane, this mucous membrane reaction is known as a *radioepithelitis* (Coutard, 1922) Repair is rapid or delayed, depending on the circumstances mentioned The columnar epithelium of the nasal fossae and trachea is considerably less radio sensitive and may not be apparently affected by relatively large doses

**Effects of Irradiation of the Gastrointestinal Tract**—Irradiation of the gastrointestinal tract results clinically in the development of diarrhea, even with relatively small doses, these effects are due to action on the small bowel and are responsible for the early adoption of a lead rubber apron as a means of protecting the radiologists

Experimental studies reveal that following irradiation of the *stomach*, there is marked diminution of the mucus and acid content of the gastric secretions even when the dose is not sufficient to produce histologically recognizable lesions (Szego, Ivy) Histologically, the irradiation of the stomach does not result in visible changes of the gastric mucosa but it affects considerably the peptic glands, with large doses, lesions may be observed in the fundic glands (Regaud, 1912) In the rabbit, the radiosensitivity of the gastric mucosa is greater than that of the skin (Engelstad, 1935)

In the *small intestine*, the main effect of irradiation is found in the glands of Lieberkuhn on the villi and on the lymph follicles (Warren) Excessive irradiation results in permanent injury, malnutrition and cachexia (Martin) First effects consist in overproduction of mucus and in hyperemia and edema, later there may be infection and inflammation loose connective tissue appears in the submucosa and progressive obstruction and perforation may result The *large bowel* is considerably less vulnerable however, large doses may result in ulceration of the mucosa (uterine radium application)

The irradiation of the *salivary glands* results in thickening of the saliva with diminution of the total amount secreted together with qualitative changes Histologically however, there is no immediate alteration Lacassagne and Gricourt noticed epithelial atrophy probably due to development of fibrosis in heavily irradiated glands, the serous elements were more affected than the mucous elements The effects on the *pancreas* and *liver* are practically nil except for massive necrosis which may occur following excessive doses but the *biliary tree* and the *gall bladder* present alterations with much smaller doses (Case)

**Effects of Irradiation of the Urinary Tract**—Doub, Hartman and Lolli ger reported sixteen cases of nephritis which developed or became evident during the course of roentgentherapy, these authors also produced experimentally an acute nephritis in dogs by direct irradiation of the *kidneys* This experimental nephritis resulted in hypertension and hypertrophy of the heart the lesions observed were those of an interstitial and vascular chronic nephritis with de



Fig 722 —Advanced malignant melanoma of the choroid. The patient had metastatic disease in the liver without regional lymph node involvement

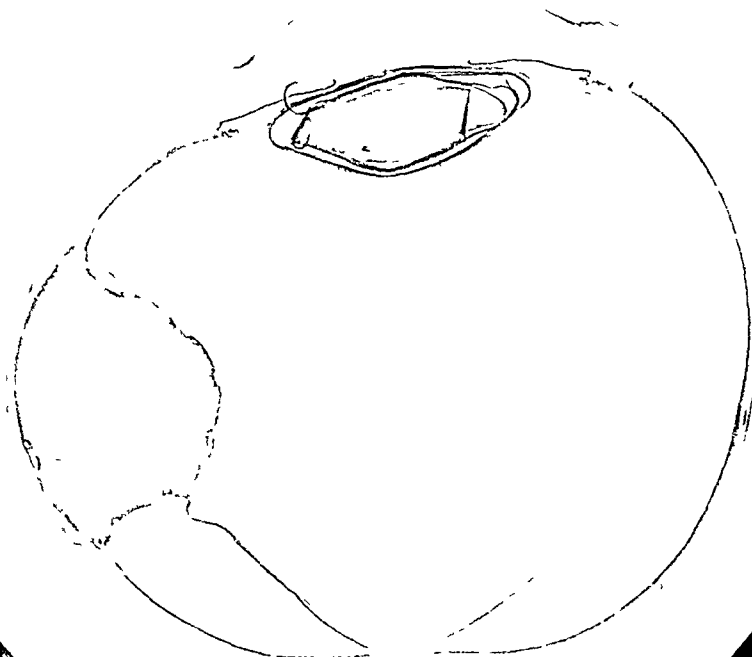


Fig 723 —Transverse section of an eye showing an early malignant melanoma of the choroid

Microscopically the malignant melanoma of the eye can exhibit many variations ranging from spindle to vesicular to epithelioid-cell type. Callender believes that a Wilder stain for reticulum is of value. If the tumor is excised sections should always be taken of the optic nerve to determine if tumor has invaded it near the point of excision. The pure spindle cell types apparently grow more slowly, while the epithelioid variety grows rapidly. If the Wilder stain brings out an increased amount of argyrophil fibers this usually means that the tumor is of the slowly growing variety.

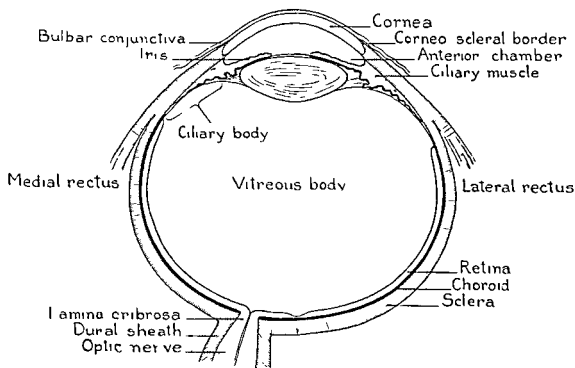


Fig. 721 — Anatomic sketch of a transverse section of the right eye. All important anatomic structures are labeled.

The *retinoblastoma* arises from the retina and may be either very flat or elevated. With increase in size it can involve the choroid where the growth may be rapid because of its rich vascularity (Fig. 724). The tumor may replace all the structures of the orbit and invade the bone. It often forms a large exophytic, ulcerated, infected mass. Necrosis is common within it and frequently small areas of calcification are seen. Microscopically the retinoblastoma is made up of immature cells called retinoblasts. These cells are small with dense nuclei and little cytoplasm and are arranged in the form of rosettes (Fig. 725). Vessel walls very often reveal hyaline degeneration and calcification (Wintersteiner). The most important point of invasion is the optic nerve. The tumor frequently invades the underlying facial bones and the base of the skull spreading directly to involve the meninges.

*Epidermoid carcinomas* arise from the corneoscleral junction and form a solid grayish white tumor. Papillomas can occur in the same area. After a long

### Clinical Evolution

The *malignant melanoma* only rarely begins on the iris where it may arise from a nevus. When the nevus turns malignant, there is increased growth and pigmentation. If the melanoma originates in the uveal tract, it causes disturbances of vision and finally complete loss of sight. The tumor may replace the eye and orbit and become a dark ulcerating infected mass (Fig. 726).

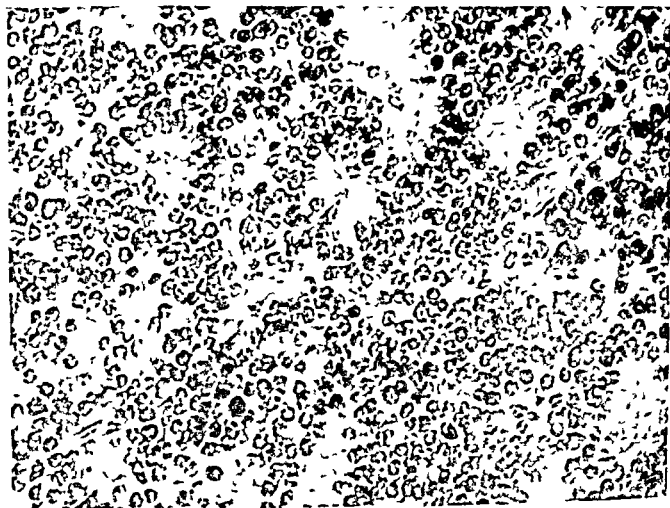


FIG. 725—Photomicrograph of a well-differentiated retinoblastoma.



FIG. 726—Advanced malignant melanoma of the eye with chemosis. A roentgenogram showed extensive destruction of the bones of the orbit. The patient died of generalized metastases to brain, lungs, and liver.

period of time, the carcinoma may invade the surrounding structures. Microscopically they are typical epidermoid carcinomas except that they do not show keratinization.

**METASTATIC SPREAD**—A malignant melanoma of the eye may have a very characteristic evolution in that a long time interval may elapse between enucleation and the appearance of distant metastasis. It is not too rare for twenty

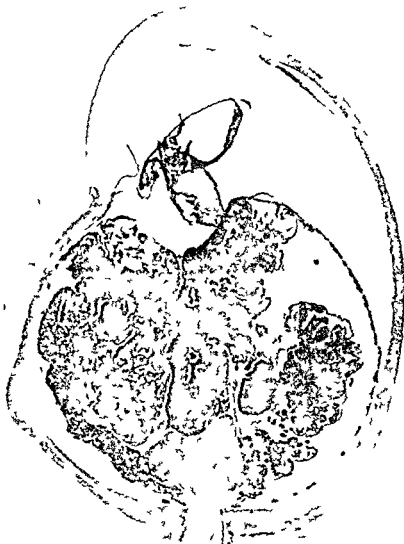


Fig. 724.—Retinoblastoma of the eye with areas of necrosis and extension to the optic nerve.

or more years to elapse before the tumor again becomes apparent invariably in the liver and fairly often in the brain. Widespread dissemination may take place. The retinoblastomas in their terminal stages disseminate widely to involve cervical lymph nodes, lungs, liver, and bone. Epidermoid carcinomas remain localized for long periods of time before metastasizing to preauricular lymph nodes.

Metastases to the preauricular and cervical lymph nodes followed by generalized dissemination of the disease are fairly common in the untreated cases (Fig 727)

The *retinoblastoma* is probably present at birth but is not clinically apparent. The first symptom may be a squint of the eye. Later a light reflex in the pupillary area may be noted followed by a diminution in vision. As the tumor replaces the eye it erupts from the orbit to form a fungating mass, ulcerated, infected and extremely painful. After the appearance of one tumor, the same symptoms fairly frequently affect the opposite eye. Ultimately, vision is lost in both eyes. Metastases to the brain and skull take place and the child usually dies blind and in considerable pain.

The *epidermoid carcinoma* of the eye is a very slowly growing tumor beginning in the region of the limbus. The evolution may take several years (Fig 728). Death from the local effects of the tumor is unusual.

### Diagnosis

The diagnosis of tumors of the eye may be difficult and at times it may be necessary to examine the eye under anesthesia particularly in children. Examination of the visual fields may be useful and transillumination may be helpful particularly for the anterior portion of the eyeball.

A *malignant melanoma* is a pigmented swiftly growing tumor which may arise in the uveal tract of the iris and cause rather rapid blindness. The diagnosis may be obscured by the presence of secondary glaucoma, uveitis, or separated retina. Examination then may reveal tumor. At times a patient who has suffered an enucleation of an eye consults a physician many years later for an abdominal complaint and presents an enlarged nodular liver. In such cases a melanoma should be suspected. For instance one of our patients revealed loss of vision and an extremely large nodular liver. Nothing could be seen on examination of the eye, but melanin was demonstrated in the urine and aspiration biopsy of the liver resulted in a positive diagnosis of metastatic malignant melanoma.

The development of *retinoblastoma* is a possibility in children of any family having a history of these tumors. The early diagnosis depends on the recognition of a squint and noticing a light reflex (Fig 729). It should be emphasized that the ophthalmic examination of the apparently uninvolved eye must be done under a general anesthetic. If the tumor is small and located near the equator or periphery it may be easily missed (Reese, 1945).

The *epidermoid carcinoma* of the conjunctiva is seen as a solid grayish-white slowly growing lesion in the region of the limbus. It may look innocuous and consequently should be biopsied for verification.

**Roentgenologic Examination**—The roentgenologic examination of an eye tumor is of no diagnostic value. An advanced retinoblastoma may present roentgenologic evidence of destruction of the bones of the orbit, and in about 75 per cent of the cases, a mottled irregular calcification is seen (Pfeiffer). The tumor can undergo spontaneous regression, with an increase of calcification.

**Differential Diagnosis**—There are several conditions which may mimic malignant melanoma of the eye rather successfully and lead to enucleation.



Fig. 777.—Malignant melanoma of the bulbar conjunctiva. One year after exenteration preauricular metastases developed but the patient has been well four years following radical neck dissection.



Fig. 778.—Epidermoid carcinoma of the bulbar conjunctiva.



ence of tumor in the optic nerve postoperative irradiation is indicated. If one eye has been removed and an early lesion is found in the other, then roentgen-therapy to this radiosensitive tumor is indicated, for in some instances the tumor may be sterilized and sight retained. It is not rational to abstain from treatment when a bilateral retinoblastoma is present. As Martin and Reese have indicated, since the child cannot be consulted, it seems only fair that his life at least should be spared. That radiotherapy may be used in preference to surgery in a primary case of retinoblastoma has never been substantiated.

Early *epidermoid carcinomas* are successfully treated by enucleation. Treatment by irradiation results in cataract, but this does not occur immediately and also may be avoided.

### Prognosis

There have been 500 cases of intraocular *malignant melanoma* followed by the American Registry of Ophthalmic Pathology. Death occurred within five years of treatment in 239 of the patients (48 per cent). Follow-up was continued on 200 patients for ten years or longer, and, of these, 66 per cent died. The pure spindle-cell type has a higher five-year survival than the tumor which has a predominance of epithelioid cells. Pigmentation has little effect upon prognosis (Callender).

In nine patients with bilateral *retinoblastoma* in whom one eye was removed surgically and the other treated by irradiation, six survived five years, four were blind (Martin and Reese, 1945). If the tumor has invaded the choroid or is extremely advanced the prognosis is very poor. About 50 per cent of the unilateral retinoblastomas are cured by surgical removal. The undifferentiated type has a poor prognosis in contrast to the relatively good prognosis of the well-differentiated type (Parkhill).

The prognosis of *epidermoid carcinoma* is quite good. Larsson reported on six patients, four of which were free from symptoms for more than five years. Of these four, three had a combination of irradiation and surgery and one had irradiation alone.

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*Disciform degeneration of the macula* produces a grayish green elevated lesion under the retina. This condition is often bilateral. The differentiation may depend on a failure of any change in the size of the scotoma as recorded by the visual fields. *Localized inflammatory lesions of the choroid, organized subchoroidal hemorrhage, angioma, and metastatic carcinoma of the choroid* can simulate malignant melanoma (Terry). Metastatic carcinoma arises from breast, thyroid and bronchogenic carcinoma most commonly. A retinoblastoma, because of its characteristic age distribution, family history, and very definite signs and symptoms, is rarely confused with other conditions. A *tuberculoma* or a *persistent tunica vascularis* may rarely be a problem in the differential diagnosis of retinoblastoma. The epidermoid carcinoma can be simulated by a *benign papilloma*. However, it should be remembered that these benign papillomas may become epidermoid carcinomas in time.



Fig. 3.—Leukocoria (white reflex) present in the dilated pupil of the right eye due to a retinoblastoma. (From Martin II and Reese A. B. Arch. Ophthalm., 1945.)

### Treatment

The treatment of *malignant melanomas* of the eye is radical excision. In an instance in which the excision was done at our hospital, a node metastasized later appeared in the preauricular area. This was excised in continuity with a radical neck dissection. Prophylactic neck dissection, however, is not indicated.

The treatment of *retinoblastoma* has been the subject of much discussion. Certainly if the tumor involves only one eye the treatment should be radical excision of the tumor and as much of the optic nerve as possible. If tumor has extensively involved both eyes then bilateral radical excision should be done, again taking as much of the optic nerve as possible. Reese examined 119 eyes enucleated for glioma with no extracocular extension. In sixty-three instances (52 per cent) the gliomatous tissue had invaded the optic nerve posterior to the lamina cribrosa and in fifty-one of these the optic nerve had not been severed distal to the tumor. If the pathologic examination reveals the pres-

because these diseases are independent processes and either one may precede the other. It is possible that Hodgkin's disease, because of its predilection for the reticuloendothelial system, may cause latent or clinically quiescent tuberculosis to become reactivated by its presence. Furthermore, if tuberculosis is a causative factor, Hodgkin's disease should be more frequent in regions where the tuberculosis rate is high. But, on the contrary, Uddstromer found that Hodgkin's disease was less common in regions where the tuberculosis rate was high than in those areas where it was not so frequent.

### Pathology

**Gross Pathology**—Practically every organ of the body has been cited as the apparent primary site of Hodgkin's disease. The overwhelming majority of cases, however, seem to originate within the lymph nodes. The lymph nodes



Fig. 730.—Frontal section of both lung and main bronchus showing partial obliteration of bronchi by massive trichobronchial lymph node replacement by Hodgkin's disease.

involved with Hodgkin's disease show strikingly significant alterations. On section their architecture is usually obliterated and they have a homogeneous grayish-yellow appearance which may or may not show zones of necrosis. These diseased lymph nodes may grow to involve adjacent structures. The cervical nodes may obstruct veins or invade the muscle. The lymph nodes of the mediastinum and hilar region are frequently the point of departure for secondary involvement of the trachea, bronchi, pleura, or lungs. The retroperitoneal nodes may involve nerves and the vertebral bodies and at times may displace or occlude the ureters. The iliac lymph nodes may obstruct venous return. Other lymph nodes lying in contiguity to viscera may invade them. Perportal lymph nodes may rarely obstruct the biliary tract.

## Chapter XIX

### HODGKIN'S DISEASE

#### Incidence and Etiology

At the present time no conclusions can be drawn as to whether Hodgkin's disease is a true neoplasm or a granuloma. A presentation of this argument would be too space consuming, but it can be asserted that in either case Hodgkin's disease is a specific entity. It is regrettable that there is a tendency to group various conditions such as lymphosarcoma and the leucemias together with Hodgkin's disease under a single heading as, for instance, that of malignant lymphoblastoma, since this identification only confuses the picture.

The true incidence of Hodgkin's disease is difficult to estimate, a few facts however may be repeated with confidence. Symmers and Barron reported 0.24 per cent of these cases among several thousand autopsies. The disease is twice as common in men as in women. This predominance in the male is increased among children where the proportion of male to female patients may be 4 to 1 (Smith). Wallhauser has called attention to the fact that although the disease may occur during any decade of life (Table LXXVIII), it is rare at puberty and

TABLE LXXVIII    AGE DISTRIBUTION  
(From Goldman, L. B.    J. A. M. A. 1940)

Decade of life	1st	2nd	3rd	4th	5th	6th	7th	8th
Number of cases	11	25	62	46	24	25	15	4

its peak incidence is between the ages of 18 and 30 years. There seems to be no unusually high incidence of Hodgkin's disease in any particular race.

The number of articles written on the causes of Hodgkin's disease attests to its unsettled etiology. Spirochetes, protozoa, cocci, and bacilli (particularly diphtheroids) have all been considered and discarded as possible etiologic factors. The attenuated strain of avian tubercle bacillus was thought by T' Sperance to be the cause of the disease, but this belief has not been supported by other authors. T'wart's intensive study of innumerable bacteriologic agents gave completely negative results. Brucellosis has been found associated with Hodgkin's disease in a rather high percentage of cases by some observers (Parsons, Wise, Forbus) but this association has not been confirmed by other workers and it is doubtful that it bears causal relationship. A virus etiology has not yet been disproved (Schoen, Grand).

Parker found at autopsy a high percentage of associated tuberculosis both healed and active with Hodgkin's disease. In Parker's series, 20 per cent of the cases of Hodgkin's disease were associated with active tuberculosis, while other forms of cancer presented an incidence of only 5.7 per cent. However this association does not indicate that tuberculosis is the cause of Hodgkin's disease.

generation of the tubules, sclerosis of the vessels, and atrophy and hyalinization of the glomeruli (Hartman, 1926). Apparently the tubules are more susceptible to injury (Domagk), but obliteration of the capillaries and atrophy of the glomeruli may follow (Willis). The *ureters* seem very little affected by irradiations.

The effect of irradiation of the *bladder* can be observed in patients receiving or having received treatment for carcinoma of the cervix. Rarely a slight dysuria develops during treatment, but cystoscopic examination seldom reveals more than congestion and edema of the mucosa. The bladder mucosa may be entirely covered with false membranes following a course of external pelvic roentgentherapy, but this is inconstant. In heavily irradiated patients, the mucosa may become telangiectatic and atrophic and be the subject of a late necrotic ulceration which is covered by mineral concretions and is long in healing. Sporadic episodes of hematuria are not infrequently observed.

**Effects of the Irradiation of the Gonads and of the Embryo**—The experimental irradiation of the *testes* results in a progressive diminution of size, attaining a minimum toward the end of the fourth week, during this time the sexual appetite of the animal is unchanged and spermatozoa are present in the sperm although in diminishing quantity. After eight weeks the spermatozoa are entirely absent, they may reappear after a shorter or longer interval or remain absent, depending on the intensity of the irradiation. There are no changes in the secondary sexual characteristics. Histologically, this is explained by the destruction of the spermatogonias which disappear within a few days and by lesser effects on the more differentiated cells of the seminiferous tubules. The destruction of the spermatogonias results in complete disappearance of the germinal epithelium after a few weeks, once the maturation of the surviving cells on the other strata has been completed, the tubules shrink and become occupied by syncytial cells of Sertoli. The interstitial cells remain intact, and thus the sterility without impotence is explained. The re-appearance of spermatogonias among the Sertoli cells and the re-establishment of spermatogenesis follow after variable intervals, depending on the dose administered and other factors (Beigomé, Regaud, 1922).

The irradiation of the *ovaries* of young women results in a permanent or temporary arrest of menstruation and development of hot flashes, anxiety, nervousness, etc., characteristic of the menopause though perhaps in a more marked degree. The sexual ardor is very variably influenced or may not be affected at all. In the experimental animal the artificial menopause may be accompanied by frigidity (Lacassagne, 1913). The irradiation of the ovary may result in the destruction of all follicles contained in the ovary, but these are very differently affected, depending on their degree of maturity at the time of irradiation. The larger, nearly mature, follicles are most affected and disappear rapidly, the small primary follicles are very radiosensitive but, because of their large number and small size, may escape a small dose, and they are responsible for the eventual restoration of menstruation. Toward the end of the fourth week, a thoroughly irradiated ovary becomes smooth and decreases in weight. The interstitial glands show very poor radiosensitivity, but the atrophy that

Lung involvement is frequently observed at autopsy. It may occur because of direct invasion of lung tissue from hilar lymph nodes and may result in intrabronchial and peribronchial spread (Fig. 730). The lymphogranulomatous tissue may involve the interalveolar walls and spread luxuriantly within the lung parenchyma. At times lobar infiltration with variable bronchomediastinal involvement together with confluent lobular foci and associated involvement

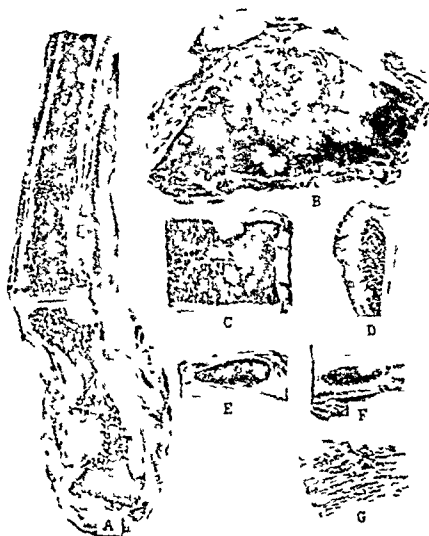


Fig. 730.—Section of different bones showing medullary and cortical involvement by Hodgkin's disease in a single patient, examined in: A, manubrium; B, lumbar vertebra; C, lumbar vertebra; D, rib; cross section; E and F, ribs; and G, normal human tibia bone. (From St. John, J. L., Arch. Path. 1961.)

of lymph nodes is present. Miliary dissemination can occur but cavity formation is rare (Bouslog). It has been suggested that in some cases of Hodgkin's disease the lung lesions may be a primary manifestation.

At post mortem examination bone involvement is also found in a large number of cases, the incidence reported depending on the thoroughness of the

examination and the number of sections taken. Uehlinger has emphasized that the involvement of bone is often a secondary phenomenon due to direct invasion from diseased lymph nodes. Involvement, therefore, of the vertebrae, ribs, and sternum is common (Fig 731). Bone involvement may also take place through the blood stream and result in pathologic alterations within the marrow cavity wherever red marrow is present, for example, the vertebrae, sternum, femoral head, and, rarely, the ribs, pelvis, and skull. Steiner felt that the distribution of bone lesions corresponded to the distribution of the reticuloendothelial system. Bone changes are predominantly osteolytic in the vertebrae and in the skull (Dresser). Osteoplastic changes, however, may be present although their gross appearance does not permit differentiation with malignant tumors, either primary or metastatic.

Involvement of the spinal cord may occur. Weil observed a high incidence of secondary invasion of the spinal canal by epidural lymphogranulomatous masses. In some cases where paraplegia had been present and radiotherapy had been given, post-mortem examination revealed only scar tissue.



Fig. 732—Massive involvement of the spleen by Hodgkin's disease.

The spleen is found involved at autopsy in about 75 per cent of the cases (Fig 732). It is not usually greatly enlarged but presents involvement in the form of nodular masses. According to Klemperei, the macroscopic and microscopic appearances of the spleen may often prove or disprove the diagnosis of Hodgkin's disease. Liver involvement occurs probably in about 50 per cent of the patients also without producing, as a rule, marked enlargement of the organ (average weight, 2,000 grams). Primary involvement of the gastrointestinal tract is infrequent, though Warren (1942) has reported thirteen cases of Hodgkin's disease apparently confined to the gastrointestinal tract. It should be remembered that practically every organ in the body has been noted at some time as being involved by Hodgkin's disease.

**Microscopic Pathology**—Hodgkin's disease, no matter where it may be present, has a sameness to its pathologic pattern. It may vary, however, within wide limits, depending upon cellularity, fibrosis, necrosis, and previous radium

tion therapy. The only cell which must be present in order to make a diagnosis of Hodgkin's disease in a lymph node is the *Reed Sternberg* cell (Fig 733). This cell may vary between 12 and 40 microns, have an irregular shape and its nucleus be lobulated or multilobed. The chromatin of the nucleus appears in dense aggregates and large nucleoli are the rule. The cytoplasm varies from eosinophilic to basophilic, and reticulum stains often reveal reticulum within it. It probably has its origin from sinus endothelium and from reticulum cells. It is often confused with other multinucleated cells and is particularly difficult to differentiate from the megalaryocyte whose nuclei are always single and whose nucleoli are fine and delicate (Jackson, 1944).

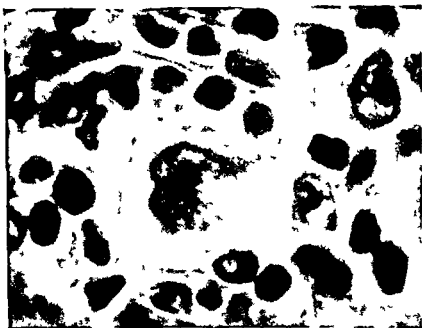


Fig. 733.—Photomicrograph of a typical Reed Sternberg cell showing multilobated nucleus with prominent nucleoli (high power enlargement).

The presence of other changes may be helpful in diagnosis but they are not specific. Fibrosis and eosinophilia are not constant, for the eosinophilia may appear and disappear during the disease and will not parallel the peripheral blood count. Necrosis is also variable. There may at times, be innumerable plasma cells and, near areas of necrosis polymorphonuclear leucocytes and reticular cells are abundant. Radiotherapy alters the histologic picture, causing at times complete sterilization. When nodes are not sterilized by the radiotherapy Reed Sternberg cells may be left surrounded by dense connective tissue (Brunschwig). Local recurrences usually take origin from nests of granulomatous islands (Gilbert, 1938).

The term "atypical Hodgkin's" should not be used. If a lesion suggests but is not diagnostic of Hodgkin's it may represent some other pathologic entity and to call it "atypical Hodgkin's" may obscure the true diagnosis. It is also true that in some cases of true Hodgkin's because of insufficient material, previous irradiation, or the unusual character of the case, a definite diagnosis



is not possible or easy. In such cases, an effort should be made to obtain additional material. Attempts have been made to divide Hodgkin's disease into various categories according to its microscopic characteristics. Jackson and Parker (1944) set up three types, the paragranuloma, the granuloma, and the sarcoma, but they indicate that transition forms may occur which are difficult to classify. Furthermore, they state that the more benign forms (the paragranuloma) may undergo transitions toward the more malignant forms, while the reverse is not true. Such a classification will be justified only if it should give a basis to a more intelligent therapeutic management or if it should furnish a good basis for prognosis. Babianitz has shown that a single group of nodes may show all variants of the pathologic picture, and for that reason alone efforts toward a histologic classification do not seem justified.

The transformation of Hodgkin's disease into lymphosarcoma, leucemia, or giant follicle lymphoma is exceedingly doubtful.

### Clinical Evolution

Invariably, the first symptom of Hodgkin's disease is painless enlargement of lymph nodes, usually cervical. In 79 per cent of Goldman's (1940) large series of cases, lymphadenopathy was the presenting symptom. He found a primary abdominal involvement in only twenty-seven of 319 patients. Table LXIX represents the sites of apparent origin in a group of 241 cases reported

TABLE LXIX  
(From Slaughter, D. P., and Craver, L. F. Am. J. Roentgenol., 1942)

	CASES	PER CENT
First enlarged lymph node		
Left cervical	99	37.5
Right cervical	55	20.8
Both sides of neck	19	6.8
Mediastinum	18	6.7
Right axilla	17	6.5
Left axilla	14	
Left inguinal	10	
Right inguinal	9	
Total	241	

by Slaughter. The cervical, supraclavicular, axillary, inguinal (Fig. 734), and retroperitoneal lymph nodes are most commonly affected. The epitrochlear, submaxillary, antebrachial, and popliteal lymph nodes are rarely involved. The disease in the lymph nodes is present for various periods of time, the nodes grow rather slowly and are often matted together but do not involve the overlying skin or become ulcerated. During the first few months or even years of the evolution of the disease, this node enlargement may be the only clinical finding not associated with any other general symptom.

Many of the symptoms which occur in the course of the disease are caused by the growth of the lymph nodes. When capsular invasion takes place, when nerves are impinged upon, when contiguous viscera are involved, and when important structures are implicated by the growth of Hodgkin's disease, a great variety of symptoms will appear. This is adequate reason for the variegated and often bizarre nature of the clinical signs. Mediastinal or tracheal lymph-



Fig. 34—A left inguinal adenopathy was the first clinical manifestation of Hodgkin's disease in this case



Fig. 73 —Typical cervical and right axillary adenopathy from Hodgkin's disease. Notice characteristic involvement of nodes of the anterior cervical chain. (Courtesy of Dr. N. Puente Duany, Radium Institute, Havana, Cuba.)

adenopathy may engender cough by pressing on invading the tracheobronchial tree. Secondary invasion of the vertebrae, the sternum, or the ribs from primarily involved nodes may cause intractable bone pain. Invasion of the epidural space through the vertebral foramina will eventually give rise to paraplegia.

Respiratory symptoms may be caused by compression of the large bronchi or by involvement of the lung parenchyma. Usually cough and dyspnea develop because of tracheobronchial obstruction. Increased dyspnea may be caused by invasion of the pleura and pleural effusion. Such effusions are practically never bloody. Rarely a cavitation of the lung will appear which may result in hemoptysis.

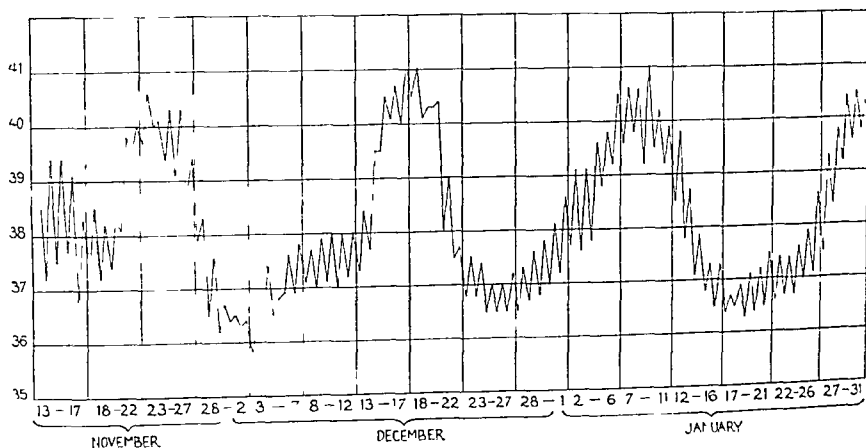


Fig. 736—Reproduction of the original temperature chart of a patient with Hodgkin's disease reported by Ebstein in 1887. Note that the time period between paroxysms of fever progressively shortens.

Certain other manifestations are worth noting. In isolated instances the first symptom may arise from a bone lesion in the form of local tenderness accompanied by a soft tissue mass over the involved bone. About 35 per cent of the patients exhibit gastrointestinal symptoms at some time during the course of the disease. In practically all such cases, however, these symptoms are not due to intrinsic lesions of the gastrointestinal tract. Goldman (1940) reported a high percentage of cutaneous manifestations ranging from simple pruritus to exfoliative dermatitis and multiple nodules. The presence of herpes zoster usually indicates impending involvement of the epidural space. These examples give some idea of the variety of specific symptoms which may appear.

General symptoms such as lassitude and weight loss usually occur only after the disease has become disseminated. In the very rapidly progressive, but fortunately rather rare, types of Hodgkin's disease, these same symptoms appear at the start. Associated anemia is frequently found when there are multiple bone lesions of the hematogenous type. It is not too infrequent to encounter some fever, particularly if there is involvement of viscera or retroperitoneal or

mediastinal lymph nodes. The Pel-Ebstein fever is often unduly dwelt upon by lecturers, but although it is present in some cases it is a relatively infrequent finding. When present, it is characterized by a rather high elevation of temperature followed by remissions which shorten progressively until the fever becomes almost continuous (Fig. 736).

As the disease progresses, the lymph node enlargement ceases to be the predominant sign. Enlargement of the liver and the spleen often becomes manifest. The general condition of the patient deteriorates with widespread visceral involvement and the late secondary effects of long continued radiotherapy.

When the disease reaches a terminal stage it may be difficult to state the exact cause of death. Not too infrequently there may be marked anemia; death may be due to secondary infections such as bronchopneumonia. If the disease is primary in the lung or within the abdomen death may result indirectly from important changes in vital organs.

### Diagnosis

In examining a patient with Hodgkin's disease the general condition should be carefully noted and all lymph node areas meticulously explored. It is important to note the patient's weight as well as all symptoms which at first may appear irrelevant. The examination should include careful palpation of the spleen and liver areas.

The enlarged lymph nodes in Hodgkin's disease are generally smooth and present moderate induration. They are usually painless and although they distend the skin, they very rarely invade it. The nodes are usually surrounded by peradenitis and have a tendency to become matted but always conserve some of their own outline giving the tumor mass a characteristic polylobated appearance.

In general the findings are concentrated in one region (neck, mediastinum or abdomen), and there is seldom discrete and generalized adenopathy characteristic of other lymphatic disturbances. As we have noted antebrachial popliteal and epitrochlear lymph nodes are very rarely involved in Hodgkin's disease.

**Poentgenologic Examination**—Roentgenograms of the chest should be taken in every case of Hodgkin's disease because of the frequent involvement of the mediastinum and lung parenchyma. Positive findings will often be revealed in spite of the absence of clinical symptoms. Wolpert found intra-thoracic involvement in thirty-five of fifty-five patients. It is imperative that oblique and lateral roentgenograms be taken in addition to the conventional ones in order that the extent of the involvement may be accurately determined. The involvement of the mediastinal nodes may be discrete or massive (Fig. 737) but the disease is usually first confined to these nodes from which it may spread to the lung. This type of involvement is sometimes observed along the course of the bronchi and interlobar or interlobular septa. Less frequently a third type of involvement may exactly mimic a primary neoplasm of the lung with replacement of an entire lobe and, under the influence of bronchial block or infection it may even cavitate. Rarely the roentgenograms will show diffuse,

scattered nodules throughout the lung *parenchyma* (Fig 738) Not too rarely will the pleura be involved and signs of pleural effusion be present

Roentgenologic evidence of bone involvement may be found in a surprisingly high number of cases Vieta demonstrated lesions of the bone in 14.8 per cent of his 257 patients upon roentgenographic examination The higher percentage of bone involvement reported from autopsies indicates that many bone lesions escape detection by roentgenographic examination Also symptoms may precede positive roentgenologic evidence of involvement for a long period of time, particularly in the blood-borne medullary lesions When the involvement occurs from contiguous lymph nodes, destruction of the cortex will be easily demonstrated Bone lesions are usually of a mixed osteoplastic and osteolytic type Lesions of the skull are invariably osteolytic (Dressei, 1936) The changes in the extremities tend to be more variable, occurring usually at the ends of long bones, most frequently in the femur Table LXX shows the distribution of bone lesions in a study reported by Dressei

TABLE LXX DISTRIBUTION OF BONE LESIONS IN HODGKIN'S DISEASE IN ORDER OF FREQUENCY  
(After Dressei, R, and Spencer, J Am J Roentgenol, 1936)

BONE INVOLVED		NUMBER OF CASES	PERCENTAGE OF TOTAL
Vertebrae		29	24.2
Cervical	3		
Dorsal	8		
Lumbar	18		
Pelvis		23	19.2
Femur		19	15.8
Skull		11	9.2
Ribs		11	9.2
Sternum		9	7.5
Clavicle		4	3.3
Tibia		4	3.3
Humerus		4	3.3
Scapula		3	2.5
Os calcis		1	0.8
Radius		1	0.8
Mandible		1	0.8
Total		120	

**Laboratory Examination**—Straube asserts that the hematologic findings in Hodgkin's disease are not diagnostic He feels, however, that early in the course of the disease the blood picture usually shows a normal leucocyte count with lymphopenia If complications occur lymphopenia with leucocytosis appears and as the disease becomes generalized, leucopenia and lymphopenia are present Wiseman, on the contrary, has found that when the disease is rather advanced, with evidence of abdominal and mediastinal involvement, the total white cell count may be elevated above 10,000 cells per cubic millimeter Innumerable articles with many divergent findings have been written on the subject Before radiation therapy is administered, the increase of the polymorphonuclear leucocytes with some increase in lymphocytes is quite constant (Falconer, Isaacs), but normal or low counts are not rare Eosinophilia is found in approximately 20 per cent of all cases but it is exceedingly variable

it changes during the evolution of the disease and may or may not coincide with pruritus. The eosinophilia rarely rises to a high figure, averaging from 4 to 6 per cent. The number of platelets and monocytes will be increased in the earlier stages of the disease. The hematologic findings of cases which have already been treated may sometimes be explained on the basis of the changes induced by radiotherapy. Because of these changes, hypochromic anemia is common terminally.



Fig 737—Massive mediastinal involvement in Hodgkin's disease

Elevation of serum phosphatase when present, is highly suggestive of bone involvement. Woodard (1940) demonstrated a high incidence of elevated serum phosphatase in patients with roentgenographic evidence of bone involvement and reported little relation between the degree of elevation and the type of lesion, whether osteolytic or osteoplastic. She concluded that if the phosphatase were elevated, it probably indicated the presence of bone pathology in spite of negative roentgenograms. Of thirty-six patients with bone symptoms but with normal roentgenograms, twenty-one had an elevated phosphatase, and in nineteen patients with roentgenologically proved bone lesions fourteen had an elevated serum phosphatase. The basal metabolic rate is usually normal in afebrile cases of Hodgkin's disease.

Gordon (1933) reported a pathogenic agent present in the lymph nodes of Hodgkin's disease, possibly a thermostable virus. When intracerebral injections of lymph node suspensions from patients with Hodgkin's disease are injected into rabbits, they produce a meningo-encephalitis which, in the opinion of Gordon, is a specific test. Controls with miscellaneous cases of leucemia, lymphosarcoma, and carcinoma caused no reaction. However, Turner (1938) found that a meningo-encephalitis could be produced in rabbits by a suspension containing a prominent number of eosinophiles (metastatic carcinoma, trichinosis) and felt that this was not due to a virus. In other words, this test was positive whenever eosinophiles were present in a lymph node in any considerable number. Therefore it probably has no specificity.

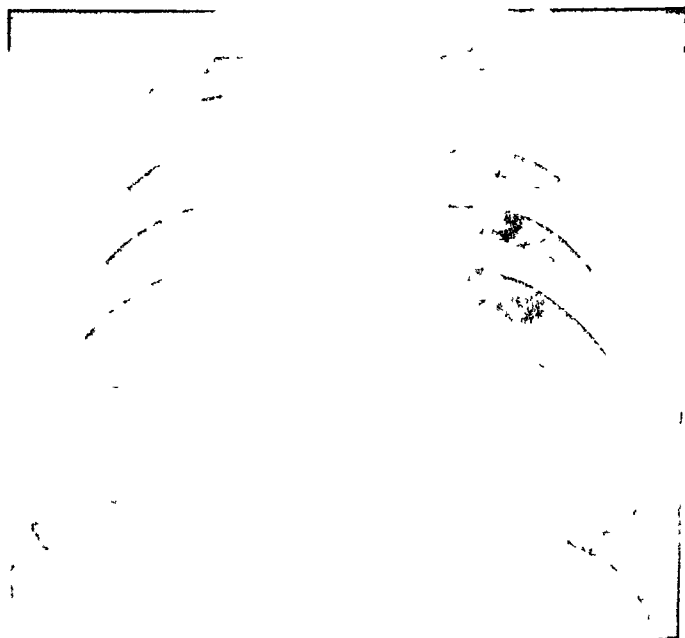


Fig. 738—Nodular involvement of the lung in Hodgkin's disease suggesting metastatic carcinoma.

**Biopsy**—A definite diagnosis of Hodgkin's disease can be obtained only by biopsy and no case, no matter how clear the clinical diagnosis may be, should be treated without benefit of it. The node selected for pathologic examination should be carefully chosen. Because of the tendency of inguinal lymph nodes to be associated with inflammation, it is preferable to choose some other node area. Moreover, very small, easily accessible lymph nodes often overlying the main tumor mass may also reveal only evidence of inflammation. Moderately enlarged nodes which can be completely excised should therefore be selected. On the other hand, incision of a bulky mass for purposes of biopsy should be avoided.

follows the disappearance of the follicles results in secondary diminution in the number and in physiologic senescence of these glands (Lacassagne)

The irradiation of the *embryo* in utero, during the first half of pregnancy results almost constantly in abortion, the irradiation during the second half may not stop the development of the pregnancy but a large proportion of malformations of the fetus result, of which microcephaly is the most common (Murphy, Goldstem)

**Effects of Irradiation of the Hemopoietic Tissues**—The irradiation of the *lymphoid tissue* of the spleen, thymus, lymph nodes, and other lymphoid structures results in important alterations the lymphoblasts of the Malpighian bodies of the spleen, of the periphery of the thymic lobules, and of the germinal centers of the nodes are most affected, but the lymphocytes disappear rapidly also, the repopulation, however, is equally rapid and it may be complete within a few days, depending, of course upon the intensity of the exposure (Heineke, Lacassagne, 1924, Rudberg)

The irradiation of the *bone marrow* results in changes affecting the leucocytic elements and the megakaryocytes while affecting very little the erythrocytic series (Heineke, Lacassagne, 1924), the possibility of a transient stimulation of erythropoiesis through forced maturation of the erythroblasts, has been suggested (Marderstein, Denstad)

Little evidence has been gathered as to the effects of radiations on the *reticuloendothelial elements* (Teneff)

**Effects of Irradiation of Other Organs and Structures**—The irradiation of the *central and peripheral nervous system* does not succeed in destroying the integrity of the nerve cell the radioresistance of the *sympathetic ganglia* has also been experimentally demonstrated (Griffith) Although degeneration of nerve cells and resulting paralysis have been reported following surgical exposure and heavy irradiation of the spine in monkeys (Davidoff), in general, the effects of irradiation of nerve tissues are the result of their action on the vascular supply, and finally, but only secondarily on the nerve tissue proper

Groover, Christie, and Merritt reported the development of a congestive reaction followed by sclerosis of the *lungs* in patients who had received radiotherapy directed to the chest, this original observation has been widely confirmed (Hsieh, Freud) The lesions occur frequently following irradiation for carcinoma of the breast, particularly when high daily doses or large single fields are used These lesions have been experimentally reproduced by Engelström (1934), who noted an almost immediate hyperemia hypersecretion of mucus and leucocytic infiltration, later there was degeneration of the bronchial and alveolar epithelium with marked signs of inflammation When this lesion does not end in death a slow progressive sclerosis takes place Warren and Gates have correlated the clinical and experimental observations and have contributed to the understanding of this process, they emphasize that the fibrosis is not a direct radiation effect and that it is greatly dependent upon variable secondary factors

In spite of the unquestionable effect of radiations in certain pathologic conditions of the *endocrine glands* their irradiation in the normal individual does



and have no tendency to be matted together. The basal metabolic rate will be elevated, the spleen will be found enlarged, and a bone marrow biopsy will often show leucemic infiltration.

A lymphosarcomatous mass with no demonstrable primary lesion offers the greatest difficulty in differentiation. In *lymphosarcoma*, however, the matted nodes become entirely united and there is no polylobated appearance. The general condition of the patient is usually affected, and when the disease has spread widely, symmetrical lymph node areas are often involved. Table LXXI shows an attempt to summarize these differential points.

TABLE LXXI. CLINICAL DIFFERENCES BETWEEN LYMPHOSARCOMA AND HODGKIN'S DISEASE

	LYMPHOSARCOMA	HODGKIN'S
Age	Common at the extremes of life	Peak between 18 and 38, rare at puberty
General condition of patient (early stages)	Often affected	Usually excellent
Pruritus	Usually not present	May precede and fairly frequently accompanies
Fever	Very rarely observed in early cases	May be found in early cases
Presence of a lesion in the upper air passages or in the gastrointestinal tract	Strong suggestion of primary lymphosarcoma of these structures	Rarely involves these structures secondarily
Lymph node involvement	Often symmetrical	Often unilateral
Cervical lymph nodes	Often bilateral, upper cervical, spinal and jugular chains	Often unilateral, lower cervical, jugular chain
Physical character	Often voluminous, ovoid masses	Often polylobated
Sternal lymph nodes (Goldman, 1945)	Practically never involved	When involved, probably Hodgkin's
Epirochlear lymph nodes	May be involved	Practically never involved
Basal metabolic rate (afebrile cases)	May be elevated	Invariably normal
Response to radiations	Great radiosensitivity, immediate response	Marked radiosensitivity, delayed response

The clinical evolution of *quant follicle lymphoma* is rather characteristic because of its slow evolution. Usually when these patients are first seen they have generalized lymphadenopathy, often have lost weight, and fairly often show moderate enlargement of the spleen. The blood count is normal and bone marrow biopsy is not remarkable. These cases, in contrast to other lymphosarcomas, rarely have involvement of the gastrointestinal tract or tonsil and often have involvement of areas in which lymphoid tissue is not prominent. Tumor nodules can arise in the lacrimal gland, the retro orbital tissue, breast, loose connective tissue of the pelvis, subcutaneous fat, scalp, and bone marrow. Chylous ascites and hydrothorax are fairly frequent. Involvement of the lungs is practically never primary in contrast to Hodgkin's disease. However, the symptoms and signs of secondary involvement of retroperitoneal lymph nodes and lungs are directly comparable with those observed in Hodgkin's disease. The basal metabolic rate may, at times, be elevated (Mayer). This type of lymphosarcoma eventually becomes widely disseminated, and circulating tumor cells in the peripheral blood may suggest the diagnosis of leucemia. This tumor responds rather dramatically to small doses of radiation. In sixty-three patients with

Any material obtained should be quickly put in a good fixative (Zenker's acetic). Proper staining allows a careful study of histologic detail (eosin methylene blue and Giemsa). Material obtained through aspiration biopsy is difficult to interpret in cases of Hodgkin's disease and for this reason the procedure is in general not indicated.

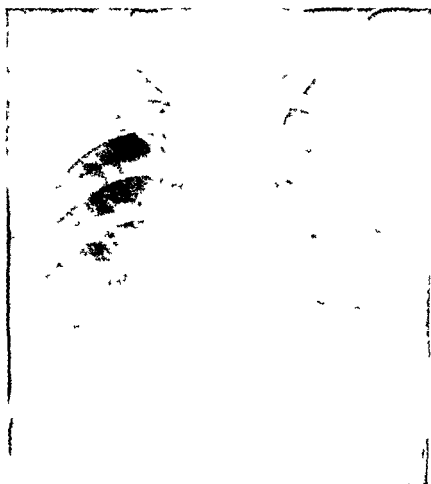


Fig. 739.—Diffuse bilateral involvement of lungs in Hodgkin's disease with peribronchovascular distribution together with mediastinal involvement.

**Differential Diagnosis**—It is sometimes possible on clinical examination to establish a diagnosis of Hodgkin's disease almost with certainty. Several considerations will help this clinical diagnosis. In the first place, the lymphadenopathy in Hodgkin's disease no matter how voluminous is usually polylobated. The nodes are not stone hard as in *metastatic carcinoma*. This mass is usually found on the anterior lower part of the neck (Fig. 735), unlike *metastatic carcinoma*, which occupies the upper portion of the neck and unlike *lymphosarcoma*, which is often found in the upper posterior cervical lymph nodes. In an early case a good general condition of the patient is always in favor of the diagnosis of Hodgkin's disease and a generalized adenopathy is against it.

*Lymphatic leucemia* can be differentiated from Hodgkin's disease in that it usually presents generalized lymphadenopathy and the nodes are usually small.

Poor administration of radiotherapy, in the timing of the treatment, the dosage, and certain particulars of the technique, may result in only a very small amount of palliation.

Because the disease has shown a marked degree of radiosensitivity and also because of the necessity of repeated treatment, it has been the custom in the past to give these patients negligible amounts of radiations. As a consequence, there were recurrences in the same areas at the same time that new additional regions were involved. The result was a rapid deterioration of the general condition and a considerably diminished life expectancy. The lymphadenopathy in Hodgkin's disease can be locally sterilized by administration of a sufficient amount of radiations. After the local sterilization, different regions will have to be treated successively, but the widespread dissemination of the disease will be retarded. When there are palpable masses in the supraclavicular region and in the axilla, for instance, it may be wise to irradiate the superior mediastinum in the absence of any roentgenographic evidence of involvement because of the unquestionably high possibilities that the disease is already present there. The same applies to superficial inguinal masses which are usually accompanied by involvement of the deeper iliac lymph nodes.

In the treatment of this disease, as in all other forms of very radio sensitive tumors, it is best to use wide fields, in order to include all potentially involved areas within a region. The use of large fields may result in the development of systemic reactions known as "irradiation sickness." Because of these reactions, large daily doses are ill advised and the treatments in general should be protracted over several weeks. Short treatments, though expeditive, require the use of a large daily dose (200 to 500 roentgens) through large fields and result in nausea and vomiting as well as in marked skin and mucous membrane reactions. When small daily doses are used (100 to 150 roentgens), there is resultant conservation of the patient's general condition, elimination of the general reactions to roentgentherapy, and minimal skin and mucous membrane reactions.

In general, 200 kv roentgentherapy is satisfactory for the treatment of these patients. Higher voltage equipment may be used but does not offer any particular advantage. The use of low voltage radiations (140 kv) has been considered advantageous in the treatment of this disease (Desjardins). The apparent greater effect of this lower quality of radiation can be explained on the basis of the greater amount of scattered radiations which results from its use over wide areas. It may be more properly said that superficial adenopathy of Hodgkin's disease does not require the use of highly penetrating radiations, but it is doubtful whether the low voltage type of radiations offers any particular advantage and, on the contrary, its repeated use over a long period of time may be less beneficial.

Favorable results have been obtained even in apparently hopeless cases. Intrathoracic masses, even when invading the pleura and lung, may totally regress (Fig 740). The treatment of bone lesions contributes prompt alleviation of pain and reparative changes. Early treatment of cases of paraplegia may be followed by motor return.

Total body irradiation with roentgen rays has been found of some relative use only in very advanced cases (Claver, Jacob). The total amount of radiations

giant follicle lymphosarcoma reported by Gall, the total duration of the disease was six years. Seventeen were alive, with an average duration of 6.8 years. The patients who had died lived 5.2 years. These figures are in contrast with the other types of lymphosarcoma in which long time survival is only possible in 2 to 3 per cent of the patients (Klemperer). Stout has recently divided his cases of giant follicle lymphoma into two varieties—a lymphocytic and a reticulum cell type, of which the latter has the worst prognosis.

When the lymphadenopathy is fluctuant particularly in the cervical region and discharging sinuses occur, *tuberculosis* may be coexistent with Hodgkin's disease. Tuberculosis of the cervical lymph nodes tends to localize to a single large node. If a superficial adenopathy is absent, one may have great difficulty in determining whether or not the patient is suffering from Hodgkin's disease. When lung lesions are present, they may masquerade as a miliary tuberculosis or even primary bronchogenic tumors (Moolten). The enlargement of lymph nodes in the submaxillary or submental regions is seldom due to Hodgkin's disease but is more often related to tumors or infections of the oral cavity. There are other diseases of the lymph nodes which may also at times be hard to differentiate from Hodgkin's disease. Hyperplastic tuberculous lymphadenitis may be confused with Hodgkin's disease (Karsner). Clinically *Boeck's sarcoid* may simulate Hodgkin's disease particularly when it involves mediastinal lymph nodes. If skin manifestations, uveitis, bone changes, or peripheral lymphadenopathy occur with it, then clinical or pathologic recognition is relatively simple. Oppenheim and Pollack reported on forty-two patients with Boeck's sarcoid, thirty-four of whom had mediastinal manifestations; the largest number of patients were 20 to 35 years of age, and twelve were Negroes. Infectious mononucleosis can be ruled out by the clinical course, the differential white count, and the heterophile antibody reaction.

In the absence of other manifestations a bone lesion of Hodgkin's disease may suggest osteomyelitis, metastatic carcinoma, or primary osteogenic sarcoma. Bone lesions may also simulate multiple myeloma, Lwing's sarcoma, or bone cyst. Gastrointestinal lesions when they are present, do not present any characteristic roentgenologic picture and cannot be differentiated from ulcerative colitis, enteritis, or obstructions of the bowel (Sherman). They are usually associated with peripheral enlargement of lymph nodes and other symptoms of Hodgkin's disease. When disease is confined to the abdominal cavity, the differential diagnosis may be particularly perplexing. Occasionally, because of its bizarre manifestations and absence of peripheral lymphadenopathy, Hodgkin's disease may be impossible to diagnose except at biopsy, laparotomy, or post mortem examination.

### Treatment

**RADIOTHERAPY**—Before the advent of radiotherapy, surgical removal of lymph nodes in Hodgkin's disease was frequently attempted and invariably followed by speedy recurrences (Ziegler). Today the treatment of choice is radiotherapy. A judicious management of this form of treatment will keep the patient in relative comfort and will offer him a reasonable prolongation of life.

Periods of remission during which the patient is apparently normal will result from the administration of radiations. However, only prolongation of life can be expected, and the best results will depend greatly upon the conscientious follow up of the patients and effective radiotherapy of new areas of involvement as they become manifest. If, under treatment, the temperature becomes normal, the pruritus ceases with a regression of all nodes, and weight is regained, these signs are favorable. If on the other hand, fever continues and the leucocyte count remains elevated or the weight further diminishes, then areas of active disease undoubtedly remain. Return of symptoms after a period of remission should lead to a thorough search for new areas of involvement.

In the presence of large mediastinal masses which have resulted in pulmonary insufficiency, administration of radiations should be very cautious. When there is coexistent pulmonary tuberculosis radiotherapy may cause a spread of this process. It is an accepted opinion that radiotherapy is contraindicated in cases of acute Hodgkin's disease. Such cases are rare and their classification as acute is only a consequence of their study from their onset to their termination. Classification in early stages is usually impossible.

Supportive therapy is indicated. Transfusions are often of great value. Foci of infection should be eradicated and the diet of these patients should be well balanced with adequate vitamin intake. Iron may also be helpful.

Surgical treatment has been recently suggested as applied to well-localized lesions: the surgical excision to be followed by intensive radiotherapy (Slaughter, Jackson, 1946). In the treatment of such a radiosensitive disease, any results obtained by such a procedure are probably to be credited to radiotherapy. If the disease is entirely eradicated by excision, then radiotherapy would be useless. If radiotherapy is indicated after excision, then the excision has not been complete. Results of such mixed therapy should not be evaluated on the basis of sporadic cases.

Nitrogen mustards have been recently used in the treatment of Hodgkin's disease (Jacobson). These compounds have unpleasant side effects (nausea and vomiting) and are bone marrow depressants. Complete aplasia of the marrow can occur. The therapeutic results in a few patients have been dramatic. Any conclusion as to the value of these new chemical compounds would be premature in view of the small number of patients treated, the short follow-up and the unpredictable clinical course of Hodgkin's disease.

### Prognosis

Permanent cures of Hodgkin's disease should be viewed with suspicion. Long-time remissions do occur. Gilbert (1944) reported on one patient who survived thirty-two years. O'Brien reported a recurrence nineteen years after an excision of lymph nodes. Gilbert emphasized how important it was not to judge results of treatment from isolated cases for there is tremendous variation in the normal clinical evolution. He divided his cases into four clinical types: (1) those which have a very slow evolution (20 per cent), (2) those presenting an average development (60 per cent), (3) a rapid form which kills

which can possibly be given to the entire body will be insufficient to contribute a permanent sterilization of the lymphadenopathy at any point and will require further segmental irradiation. The intravenous injection of radioactive phosphorus has not been successful (Warren 1945)

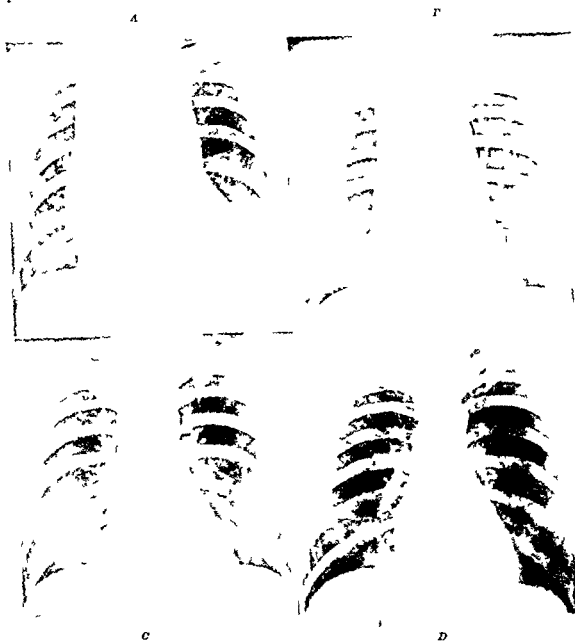


Fig. 40—A Hodgkin's disease of the mediastinum after roentgenotherapy, was started. B Same case two weeks later. C Same case four months after completion of treatment. D Same case fifteen months after completion of treatment. The patient has remained without further manifestations of the disease for three and one half years.

Pregnancy may occur during the course of the disease. According to Gilbert (1945), a therapeutic interruption of pregnancy is indicated when the disease is in an active phase. If the disease is not in an active state pregnancy may be allowed to continue, radiation therapy to the abdominal cavity or pelvis would not be permissible during the last six months of pregnancy because of danger to the child.

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brutally within a matter of months, and (4) an exceedingly fast moving variant which causes death in a few weeks.

The prognosis of Hodgkin's disease is thought to be less favorable in children than in adults (Smith). The presence of bone lesions is not of prognostic significance (Vieta). Primary or secondary gastrointestinal involvement gives a poor prognosis according to Jackson and Parler (1946). Cases presenting a paraplegia have, in general, an unfavorable course in spite of treatment and the disappearance of the disease from the spine (Weil). Jackson and Parker (1946) feel that there is a definite relation between histopathologic variants and the prognosis. Goldman (1940), on the contrary, stated that "many of the more cellular types ran prolonged courses while those exhibiting fibrous reaction had a short duration and vice versa." Slaughter also failed to find any correlation between the pathologic features and the prognosis. Table LXXII illustrates

TABLE LXXII LONG TERM RESULTS PATIENTS AT THREE AND FIVE YEAR PERIODS OF SURVIVAL  
(From Gilbert P. *Progrès de la Suisse Rom.* 1944)

AUTHORS AND YEARS	PERIOD OF OBSERVATION	NUMBER OF CASES	NUMBER AND PROPORTION OF PATIENTS LIVING AND WELL	
			MORE THAN 3 YEARS	MORE THAN 5 YEARS
De jardins and Ford (U.S.A.) (1923)	1915-1920	73	10 (13.7%)	7 (9.8%)
Holfelder and Hummel (Frankfort)	1920-1929 1920-1927	73 (f) 52 45	19 (36.6%)	8 (17.7%)
R. Gilbert and Babaianz (Geneva)	1920-1937 1920-1937	52 52	33 (63.5%)	24 (46.0%)

Desjardins and Ford specified that the cases observed from 1915 to 1920 received variable types of treatment without any systematic method. After 1920 the patients received methodical treatment. One can see that the proportion of long term results progressively increased and that they show the progress realized since 1920 in techniques of irradiation.

the three and five year survivals attainable in the treatment of this disease as well as the unquestionable progress which has been made in the past thirty years by a better understanding of radiation therapy and its judicious administration.

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not cause either any constant physiologic effect or important histologic change. Depending upon the species and age of the animal of experimentation and upon the method of irradiation used, inconsistent and consequently controversial findings have been reported after irradiation of the thyroid and parathyroid glands (Zimmein, Walters), of the suprarenal glands (Cottenot, Rogers), and of the pituitary gland (Lawrence, Lacassagne, 1935).

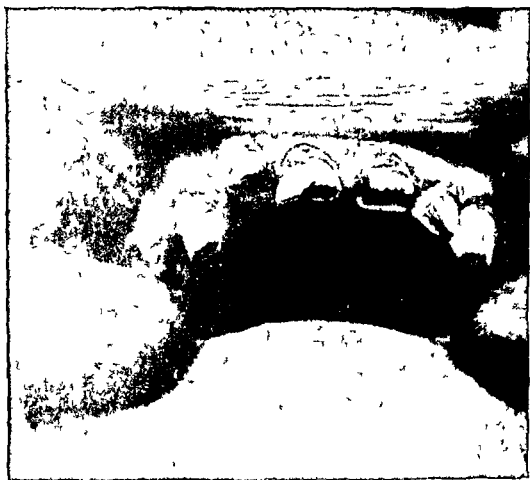


Fig. 20—Dental lesions observed following treatment for a carcinoma of the subglottis (From Regato J. Am J Roentgenol, 1939)

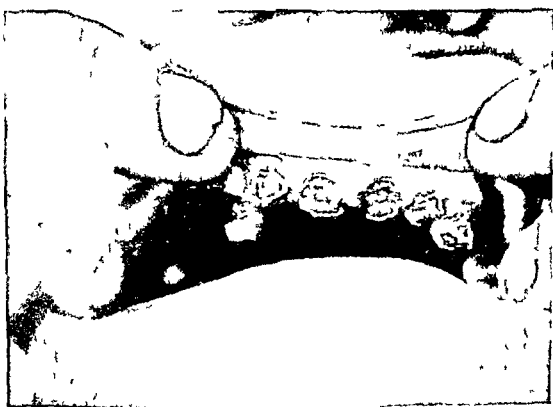


Fig. 21—Same patient two years later (From Regato J. Am J Roentgenol 1939)

Normal adult *cartilage* is not noticeably affected by radiations, but the growing cartilage, such as that of the epiphysis of long bones, may be considerably affected (Bisgard). Growing bone of the young individual is also retarded in

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## Chapter XX

### LEUCEMIA

Leucemia, for practical purposes, may be considered as a form of cancer of the hemopoietic organs. The disease affects primarily the bone marrow and the lymphatic and reticuloendothelial systems and results in a disorderly overproduction of leucocytes. It may manifest itself by an increase in the number of leucocytes in the circulating blood but occasionally is accompanied by a normal or subnormal blood picture (subleucemic leucemia). A leucocytosis with or without the presence of young forms, however, is not pathognomonic of leucemia. It can be due to various causes such as infection (leucemoid reaction) or to circulating tumor cells (leucosarcoma).

Table LXXIII is an attempt to simplify the classification of leucemia. It is realized that this classification can be criticized, but we believe that it is a usable one.

TABLE LXXIII CLASSIFICATION OF LEUCEMIAS

CELL OF ORIGIN	SPECIFIC TYPE OF LEUCEMIA	SYNONYMS
Myeloblast	Myelogenous leucemia	Myelocytic, myeloblastic, myeloid, or neutrophilocytic leucemia, myelosis
	Chloroma (a variant of myelogenous leucemia)	Chloroleucosarcoma
	Eosinophilic leucemia Basophilic leucemia	Eosinophilocytic leucemia Basophilocytic leucemia
Lymphoblast	Lymphogenous leucemia	Lymphoblastoma, leukemicum, lymphadenosis, lymphocytic, lymphoblastic, or lymphatic leucemia
Debatable origin questionably from reticuloendothelial system, plasmocytoblast, or lymphoblast	Plasma cell leucemia	Plasmocytoma with leucemia or multiple myeloma with leucemia
Monoblast	Monocytic leucemia	Reticulum cell leucemia, reticulosis, reticuloendotheliosis, reticulosarcoma, histiocytic leucemia

#### Incidence and Etiology

Leucemia is a relatively rare condition. At the Cook County General Hospital it was present in only 0.86 per cent of 14,000 autopsies. Chronic myelogenous leucemia is most frequently found in individuals between 20 and 60 years of age, the highest incidence occurring between 25 and 30 years. About two-thirds of all cases are found in males. Chronic lymphogenous leucemia is prevalent between 45 and 60 years of age and about three-fourths of all cases are in males. Acute lymphogenous leucemia occurs most frequently in the first five years of life (Fig 741). Acute myelogenous and monocytic leucemia may

occur in children as well as in older persons but is rare after the age of 50 years. There seems to be a lesser incidence of leucæmia among Negroes (Wintrobe, 1942).

The percentage distribution of the various types of leucæmia differs somewhat in statistics reported by various authors. Some of these discrepancies are undoubtedly due to disparities in diagnosis. It is possible that some variation may be due to geographic differences in distribution. Moore's percentage of 132 cases of leucæmia is as follows: sixty-five lymphogenous (49 per cent), forty-four myelogenous (34 per cent), and twenty-three monocytic (17 per cent).

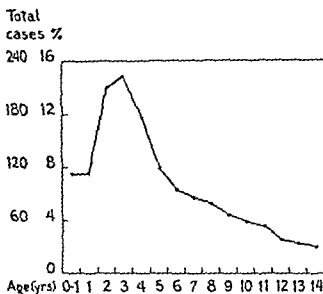


Fig. 741—Age incidence of 1500 patients with acute leucæmia. (From Cooke J. V. J. A. M. A. 1942)

Leucæmia occurs spontaneously in many varieties of fowls and mammals. In the fowl (with the exception of the lymphogenous type) it may be transmitted by intravenous or intraperitoneal injection of emulsions of cells or even of cell free filtrates (Ellerman). It has also been shown that immunization can be obtained. The etiology of the lymphogenous type of leucæmia is therefore probably a virus. Leucæmia in mice produces anatomic changes which have great similarity to those observed in man (Furth, 1935), but in contrast to fowl leucæmia, transmission of mouse leucæmia is impossible except with live leucæmic blood cells. By the process of inbreeding mice strains can be developed with a high percentage of spontaneous leucæmia (Richter 1929). The incidence of leucæmia can be further increased in these animals by the use of carcinogenic agents and also by means of radiations (Brues, Mider, Furth, 1936). Furth has demonstrated that in lymphogenous leucæmia the abnormal cells were first observed within the splenic pulp and in the reticulum meshes of the lymph node. He felt that the origin of this type of leucæmia was multicentric and that involvement of the bone marrow occurred later. This is in contrast to myelogenous leucæmia in which the changes within the bone marrow probably occur first.

There have been about a dozen instances of leucemia in man which have been reported following exposure to benzol (Penati, Selling, Falconer, 1933, Mallory). There seems to be a marked variation in individual susceptibility to benzol, but benzol poisoning and the production of leucemia are still questionable (Opie). There is no doubt that there is an increased incidence of leucemia in individuals exposed to various forms of radiations including radium, mesothorium, thorium X (Hueper), and also roentgen rays. March reported that in the United States during a fifteen-year period, eight radiologists died of leucemia, this incidence being ten times as great as in physicians not concerned with this specialty. During the last few years, leucemia has shown a spectacular rise in frequency. Since 1940, over 5,000 individuals have died of leucemia each year in the United States. It seems rather unlikely that this entire increase can be accounted for on the basis of better diagnostic acumen, or on the basis of changes in age distribution in the population, for the increase has occurred in every age group (Sacks). Increased industrialization (benzol, aniline dyes, arsenicals), the use of new drugs, and the greater exposure to numerous chemicals may be responsible (Dameshek).

### Pathology

**Gross Pathology**—The pathologic alterations in all types of chronic leucemia tend to involve many systems and if all the changes were tabulated, the changes observed would be encyclopedic. For the exception and bizarre findings, the monograph of Forkner can be consulted. The pathologic changes are mainly of two types—those which affect the blood-forming organs, particularly bone marrow, spleen, and lymph nodes, and the changes due to infiltration. The bone marrow is invariably hyperplastic and reddish-gray in color. The degree of enlargement of lymph nodes, spleen, and liver varies with the different types of leucemia. In chronic lymphogenous leucemia, generalized lymphadenopathy is frequent. The extent of involvement of various lymph node groups varies, but it is common to see peripheral enlargement of all lymph node groups and mediastinal and retroperitoneal lymph nodes are usually not enlarged at first but may show a minimal amount of replacement later. Moderate generalized lymph node enlargement is present terminally in myelogenous leucemia. The liver and spleen are invariably enlarged in chronic leucemia, usually but not invariably the greatest prominence is in the myelogenous type (Krishbaum). The enlarged spleen frequently shows perisplenitis with numerous adhesions. Infarcts of varying ages may be found in the myelogenous variety but are also observed in the lymphogenous. On section of the liver, diffuse infiltration manifested as grayish white areas measuring only a few millimeters will be seen in the myelogenous type, whereas in the lymphogenous variety these areas of infiltration are most prominent in the portal zone (Fig. 742). Cut section of the spleen shows this same type of infiltration and obliteration of architecture associated with various degrees of fibrosis. Leukemic infiltration is common in the kidneys and is invariably bilateral with enlargement of the organ.



Fig. 4.—Extensive infiltration of the liver in a case of chronic lymphatic leukemia. Note the limitation of the grayish white leucemic infiltration to the portal areas.



Fig. 5.—Liver in a case of chronic lymphatic leukemia. The large, dark mass in the center of the top image is a large, dark, irregular mass, possibly a large vessel or duct, surrounded by a lighter, granular background. The bottom image shows a similar view with a more extensive, lighter-colored area on the left side, possibly indicating a different stage or type of infiltration.



Leucemic infiltration of the gastrointestinal tract is common in the lymphogenous variety and is most prominent in the stomach and ileum where lymphoid tissue is abundant (Fig 743). The changes present may result in swelling of the folds of the stomach which resembles cerebral convolutions. In the ileum there may at times be atrophy of the overlying mucosa followed by secondary ulceration of nodular areas. Leucemic infiltration of the skin is present particularly in the lymphogenous form of leucemia.

Evidence of hemorrhagic tendencies as manifested by numerous ecchymoses and petechiae is common. Death may rarely occur from hemorrhage either into the gastrointestinal tract or into the brain. Fluid is commonly found in the pleural cavities and abdomen and a terminal bronchopneumonia is a common complication. Leucemic infiltration of the kidneys associated with pyelonephritis may lead to kidney failure and death. Central nervous system involvement is not unusual and leucemic infiltration in the brain is manifested by grayish nodules surrounded by areas of hemorrhage.

In *acute lymphocytic* the gross findings vary only slightly depending on the type of leucemia. In acute lymphogenous leucemia there is a greater tendency to lymph node involvement than in the acute myelogenous and monocytic varieties. The liver is invariably enlarged in all cases. The spleen is also enlarged but not nearly as much as in the chronic forms of leucemia; it may even be small in the acute monocytic variety. The bone marrow is hyperplastic in all cases. Evidence of bleeding phenomena may be present in all types with petechiae, ecchymoses and hemorrhages into the brain, gastrointestinal tract, lungs and elsewhere.

In *acute myelogenous* a variety of acute myelogenous leucemia green color in the tumor masses is usually present due probably to a lipochrome (Kandel). According to Goodman this pigment may be an intermediary product in the breakdown of hemoglobin to bilirubin. The pigmentation disappears an hour after death but can be made to reappear by hydrogen peroxide. With chloroma there is invariably widespread invasion of many organs and particularly striking are the retro-orbital tumor masses and the changes in the skull and thorax. The skull was involved in 73 per cent of Rothschild's patients with masses infiltrating into the dura, paranasal sinuses, the orbit, nerves, scalp, and subcutaneous tissues. There are large yellowish-green masses of tumor growing beneath the sternum invading the pleura, muscles and, at times, the myocardium. The kidneys usually show diffuse or nodular greenish tumor tissue, the spleen and liver are usually normal in size and the bone marrow is hyperplastic.

**Microscopic Pathology**—The most important changes will be found in the bone marrow. In lymphogenous leucemia there is a homogeneous replacement by lymphoid elements. In myelogenous leucemia the bone marrow shows increase of myeloid elements with numerous eosinophilic myelocytes. There is a shift to younger forms and a striking decrease in percentage of nucleated red cells. Proliferation of leucemic cells in the bone marrow may extend to the Haversian canals and thence to the periosteum. Because of these infiltrative changes,

pressure atrophy and rarefaction of trabeculae within the marrow with subsequent destruction of the cortex can occur

The study of all types of leucemia reveals variable degrees of infiltration of various organs, depending upon the type of leucemia. In this infiltration it is common to see destruction of normal tissue and replacement by masses of leucemic cells. These leucemic cells are often present in increased numbers within the blood vessels. Under the high power, immature forms can be identified. In the lymphogenous variety the infiltration is present where lymphatic tissue is most prominent and is consequently very diffuse predominantly in



Fig 744—Leucemic infiltration of the skin of the scrotum in a patient with chronic lymphogenous leucemia

the submucosa of the gastrointestinal tract, particularly stomach and ileum. In these areas the normal follicles are erased and replaced by a homogeneous mass of lymphoid cells, many of them immature. The same process is present in the Malpighian zones of the spleen. In the liver there is a localization of the leucemic process around the portal areas in lymphogenous leucemia, but the infiltration is diffuse in chronic myelogenous leucemia. Lung involvement is found at autopsy in 30 per cent of all patients (Falconer, 1933). Leucemic infiltration of the skin is occasionally present (Fig 744). Hemorrhagic phenomena

are common and there may be small areas of thrombosis. Extramedullary hemopoiesis in liver, spleen and lymph nodes may be seen.

The central nervous system is often involved and occasionally also the cranial nerves, perineural spaces, meninges, and pial vessels. The areas of leucemic infiltration of the brain often show surrounding hemorrhage (Diamond). The vascular lesions observed in the brain may be due to thrombosis of vessels by leucemic cells. Not too infrequently the walls of the vessels are invaded and leucemic infiltration spreads out into the brain substance (Fried). Schwab tabulated the neurologic findings in a large series of cases and found frequent cerebral invasion and cerebral hemorrhage, he also found frequent invasion of the cranial meninges and cranial nerves. Cranial nerve nuclei were involved in about one-sixth of the cases.

### Clinical Evolution

The chronic forms of leucemia usually have an insidious onset, and it is difficult to establish exactly how long the disease has been present before the first symptom occurs.

In *chronic lymphogenous leucemia* the outstanding first sign is the enlargement of the lymph nodes, particularly in the cervical region. Because of this peripheral abnormality, this variety is probably diagnosed earlier than myelogenous leucemia. It is estimated, however, that the disease may progress from one to one and one-half years before it is recognized (Wintrobe 1939). The lymph nodes do not enlarge rapidly and rarely measure more than 5 cm. in transverse diameter (Fig 745). The spleen is usually enlarged several fingerbreadths below the costal margin. The blood count may be normal.

In *chronic myelogenous leucemia* there is rarely any enlargement of the lymph nodes in the early stages and the disease may be present for from two to five years before it is recognized. The outstanding symptom is the considerable enlargement of the spleen which extends sometimes to the pubis and causes a sensation of heaviness and dragging. Tenderness of the sternum, usually limited to the gladiolus, is found in a majority of the patients (Craver, 1927), but this is not pathognomonic of the myelogenous variety.

In later stages of both varieties of chronic leucemia, the symptomatology and the clinical findings are protean in nature because of the widespread involvement of multiple organs (Table LXXIV). Anemia is usually manifested by pallor and is due to replacement of the red-blood-cell-forming organs of the bone marrow by the leucemic elements. There is also an increased metabolism, which added to the anemia, produces tachycardia, weight loss, intolerance to heat, perspiration, and dyspnea on exertion. If there is a latent cardiac disease in a patient verging on congestive failure or some asymptomatic narrowing of the coronary arteries these two factors may cause congestive heart failure or angina pectoris. All these symptoms may gradually disappear with treatment, but with involvement of the central nervous system cranial nerve palsies may occur (Schwab), sometimes accompanied by pyramidal signs. Priapism some times but not always accompanied by thrombi of the veins of the corpora cavernosa may also be present. Cases of leucemia may rarely begin with pri-

mary manifestations related to other organs such as the prostate (Flaherty) or female genitals (Hauptman). During the course of the disease, retinal hemorrhages, edema of the disc, sudden blindness, and leucemic retinitis can appear (Goldbach).

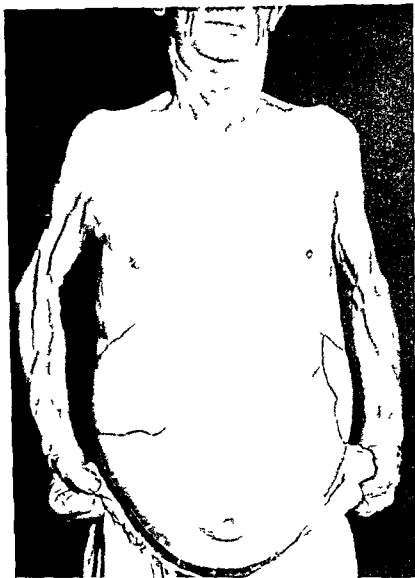


Fig. 745.—Patient with chronic lymphatic leucemia. Note enlargement of all node group and enlargement of spleen and liver as outlined. (Courtesy of Dr. E. H. Reinhard, Department of Medicine, Washington University School of Medicine, St. Louis, Mo.)

Intense pain may result from infarction particularly of the spleen. Involvement of other abdominal organs may simulate an acute abdominal condition. Leucemic infiltration of the skin may be present particularly in the lymphogenous variety (Fig. 744). However, a considerably larger number of patients develop skin lesions entirely unrelated to the leucemia, probably due to lessened resistance to infections. Infection takes place most often in the lymphogenous variety.

TABLE LXXIV CLINICOPATHOLOGIC CORRELATION OF LESIONS AND SYMPTOMS IN CHRONIC LEUCEMIA

Lymph node enlargement	Mediastinum Retroperitoneal	Cough, dyspnea Gastrointestinal disturbances, distention, abdominal pain
	Elsewhere	Pressure symptoms
Spleen	Enlargement	Dragging sensation
	Infarct	Acute pain
Bone involvement	Bone marrow replacement	Local bone pain (periosteal involvement), anemia, pallor, fatigue, palpitation, hemic murmurs
	Increased metabolism plus anemia	Perspiration, easy fatigue, intolerance to heat, weight loss, increased appetite, increased pulse rate (not as marked as in hyperthyroidism), cardiac failure, angina pectoris
	Thrombopenia	Petechiae, purpura, hemorrhage
Gastrointestinal involvement	Stomach and ileum	Diarrhea, nausea, vomiting, occult blood (rarely gross hemorrhage)
Nervous system (Schwab)	Brain hemorrhage	Paraplegia and pyramidal tract symptoms
	Cranial nerve nuclei	Cranial nerve paralysis
Kidneys (Merrill)	Infiltration, nephrolithiasis (Uric acid)	Renal colic, renal failure, pyuria
Lungs (Falconer)	Diffuse infiltration	Dyspnea

Death often occurs in chronic leucemia because of infection, particularly bronchopneumonia, but may also result from sudden cerebral or gastrointestinal hemorrhage (Jackson, 1939). Heart failure is not unusual as a cause of death.

*Acute leucemia* is most often encountered in children. The onset is often sudden, and a diagnosis is seldom made before the disease has run at least half of its short course. About one-third of all cases have a history of hemorrhage after some minor operation such as a tonsillectomy or tooth extraction (Warren). Fever, pain in the bones and joints, petechiae, hemorrhages, and severe secondary infection are characteristic findings. Very often the laryngologist is consulted because of sore throat, enlarged tonsils, or changes in the oral and pharyngeal mucous membrane. The differential diagnosis of any type of acute leucemia is an academic problem because there is no difference in its response to treatment. Exclusive of peripheral blood and bone marrow studies, there are a few clinical findings which have a variable significance, but none of them are absolute. The lymphogenous type often occurs in children under 10 years of age but may occur at any age. The enlargement of the spleen is invariably present in all types, but this is usually of moderate degree and often the spleen is not even palpable. In the acute lymphogenous variety, the lymph nodes are generally enlarged, but cases have been seen without any enlargement. Monoeytic leucemia frequently shows enlargement of the cervical lymph nodes, which may be tender because of coexisting oral infection. The most important differential point in monoeytic leucemia is the change present in the oral cavity and pharynx where there is diffuse inflammation, ulceration, necrosis, and severe bleeding (Evans, Kaufmann). It is not unusual in a fair percentage of both lymphogenous and myelogenous varieties to find a subnormal white blood

its growth, and the more so the younger the subject (Dahl), but the effect of irradiation of *adult bone* is usually a consequence of vascular changes, such as the avascular necroses of the neck of the femur which may occur after irradiation for carcinoma of the cervix through lateral fields (Fig 619). Osteonecrosis results from excessive weight or trauma over a devitalized bone. In other areas osteonecrosis may result from secondary infection of a heavily irradiated bone. Growth of *teeth*, without damage to the teeth themselves, may be retarded by irradiation (Recamier). In patients who survive several years after irradiation for tumors of the oral cavity or pharynx, a peculiar form of dental caries (Figs 20 and 21), most often painless, finally results, causing complete amputation of teeth (Regato 1939). Experimental work in animals with continually growing teeth shows evidence of damage of the odontoblasts of the dentine following irradiation (Leist), but in man the lesions most frequently observed clinically are probably due to an indirect action (through qualitative changes of the saliva) since many occur in the absence of irradiation of the teeth themselves or even of the jaw (Regato 1939).

The irradiation of *muscles* the smooth as well as the striated variety does not bring about any appreciable changes unless the doses are excessive. The frequent irradiation of the *myocardium* in clinical radiotherapy has stimulated careful study of possible injury to it (Hartman 1927) but the organ has a great tolerance (Desjardins).

The irradiation of the *eye* may result in the development of a cataract. The lens is the most radiosensitive part of the organ, but a normal adult human eye may receive a rather large amount of radiations under certain conditions without development of a cataract for several years (Regato, 1937). Both the quality and the intensity of the irradiation plus personal factors are involved.

The effects of radiations on the *connective tissue* everywhere in the body are most important, although little is known about them, vasodilatation increased diapedesis, and exudation may be the result of irradiation of small vessels and in addition, there may be alterations of the fibroblasts with edema and hyalinization of the collagen and elastic fibers. This inflammatory phase may be progressively replaced by fibrosis resulting in secondary atresia of the vessels and consequent devitalization of the tissues, but these final effects are very variable depending on several factors.

### Radiophysiologic of Malignant Tumors

The irradiation of malignant neoplastic tissue may result in the almost immediate disappearance of all cells in mitosis and, after a short period of time in an abnormally large number of *degenerative mitoses* followed by death of the cells from accelerated maturation (Clunet). Whenever this phenomenon can be brought about repeatedly by new irradiations complete destruction of the tumor can be expected but in a large number of malignant tumors, intensive irradiations may not give rise to such a response and the tumors may continue to grow in spite of irradiations. *This difference in response to irradiation, the different radiosensitivities of malignant tumors, is primarily an attribute of their cell of origin*

specialized techniques in the laboratory. Quite often the information received in this manner will also help in establishing a prognosis and in regulating the treatment.

**Leucocytosis**—There is, in leucaemias, a frequent rise in the number of circulating leucocytes. However, the characteristic feature of this disease is the presence of immature cells which are not normally found in the circulating blood. Although immature cells have been seen in other diseases, blast cells in large numbers are present only with leucemia. In chronic lymphogenous leucemia, the rise in the number of circulating leucocytes seldom reaches the high values sometimes seen in the myelogenous variety. The total leucocyte count frequently varies between 100,000 and 200,000 per cubic millimeter. The overwhelming majority of these usually are adult lymphocytes presenting very little cytoplasm. Immature lymphocytes are observed but in a small proportion. In chronic myelogenous leucemia, the leucocytosis is usually high and may reach a million white cells per cubic millimeter. The majority of these cells are polymorphonuclear leucocytes and, in addition, there are a great number of metamyelocytes and myelocytes, most of which are neutrophilic. Eosinophilic leucemia is extremely rare (Bass, Friedman), and before a diagnosis is made, it should be remembered that eosinophilic myelocytes are frequently present in myelogenous leucemia, and also that basophiles and eosinophiles may be present in large quantities in the circulating blood of other conditions. Plasma-cell leucemia is also very rare but may present itself as an acute or subacute variant (Moss). Basophilic leucemia has been described.

In acute monocytic leucemia, a rise in the leucocyte count is usually present, but in the lymphogenous and myelogenous varieties of acute leucemia there may be a normal number of white cells or even leucopenia. On careful examination of the blood, however, it will often be found to present an unusual number of immature leucocytes. Table LXXV gives some of the outstanding

TABLE LXXV CYTOLOGIC DIFFERENTIATION OF THREE VARIETIES OF ACUTE LEUCEMIA  
(From data by Wintrobe)

LYMPHOGENOUS VARIETY	MYELOGENOUS VARIETY	MONOCYTIC VARIETY
Predominant cell is lymphoblast (50 to 90 per cent) with round or oval nucleus and coarse, granular, or "stippled" chromatin and one or two nucleoli, chromatin is arranged compactly about the edges of nucleus and nucleoli, most other cells lymphocytes, few neutrophilic leucocytes	30 to 60 per cent of leucocytes immature, majority myeloblasts or undifferentiated myelocytes, round or oval nuclei with fine chromatin condensed around edges, several nucleoli, cytoplasm blue with few or no granules, neutrophilic polymorphonuclear leucocytes scarce, Auer bodies or mitotic figures may be found	Large numbers of monocytes (about 60 per cent) with irregularly shaped nuclei and very fine reticular chromatin, nucleoli inconspicuous, cytoplasm grayish blue with innumerable, fine, dustlike granules, irregular cell boundaries, remaining cells lymphocytes and polymorphonuclear leucocytes, but few myelocytes, myeloblasts, or plasma cells

cytologic differences for the diagnosis of specific types of acute leucemia. The differentiation frequently remains difficult, however, and usually special study will be necessary to establish the diagnosis.

cell count when the patient is first seen. The anemias coexisting with all are usually normocytic. Platelets are uniformly depressed.

In chloroma, a variant of acute myelogenous leucemia, the yellowish green appearance of the tumor masses together with extreme anemia and exophthalmus may suggest the diagnosis.

In all acute leucemias there is often a prodromal period of weakness and malaise, followed by prostration, high fever, and tachycardia. Death may occur because of pneumonia, circulatory collapse, infection, or hemorrhage. Remissions in acute leucemia have been observed but they are usually of short duration (Jackson, 1931).

### Diagnosis

The clinical diagnosis of leucemia is usually quite easy. The patient may come to the physician for the first time because of bleeding following a tooth extraction. It is also quite common for the patient to discover a large mass in the upper abdominal quadrants (when bathing). A thorough clinical examination, blood studies including supravital staining, and bone marrow aspiration are sometimes necessary to solve certain difficult cases.

**Clinical Examination**—A careful palpation of the neck, axillas, and in guinea and epitrochlear regions is always indicated. The enlarged spleen is usually easy to palpate and often can be percussed beneath the ribs. Its dimensions should be carefully noted. A light percussion may reveal the presence of sternal tenderness which is frequently found in myelogenous leucemia. Evidence of an abnormal tendency to bleed may be found in an examination of the eye grounds, oral cavity, and skin. By placing a blood pressure cuff on the arm and raising the air pressure within it above the diastolic mark, a shower of petechiae may appear in the forearm after a relatively short interval (Rumpel-Leede phenomenon). The examination should include a search for skin and neurologic manifestations.

**Roentgenologic Examination**—A roentgenologic examination of the chest is indicated in all patients with leucemia to detect possible mediastinal lymph node involvement and infiltration of the lung. Roentgenographic detection of bone involvement is seldom possible in chronic leucemia. Craver (1935) reported roentgenologic bone changes in only six of eighty-six patients with leucemia. Generalized osteoporosis is very seldom seen but areas of rarefaction are sometimes noticed near the epiphysis and this may lead to spontaneous fractures (Frb). Bone changes are frequently observed in children. These changes are usually osteolytic but can be mixed in character. Ritz described a narrow zone of diminished density proximal to the metaphysis in 70 per cent of his cases of leucemia in children. There may also be subperiosteal proliferation in the juxta-articular portions of this bone which may suggest a primary malignant bone tumor (Apitz 1938). In chloroma generalized osteoporosis may be present particularly noticeable in the bones of the skull.

**Laboratory Examination**—Although a clinical diagnosis of leucemia is frequently possible, the confirmation of this diagnosis will need the support of laboratory examination. In other instances the diagnosis is only possible through



(with a 15-gauge needle) can be done and the material obtained can be studied by the supravital stain and conventional stains and by fixed tissue sections. The bone marrow should be placed preferably in Zenker's acetic fixative and stained with eosin methylene blue or Giemsa. In early cases of chronic lymphogenous leucemia, the bone marrow may appear normal except for a few islands of adult lymphoid cells, but, as the disease develops, a complete replacement occurs. In the myelogenous variety there is distinct hyperplasia and overgrowth of normal bone marrow elements by immature cells of the myeloid series. Myelocytes are particularly prominent. After considerable irradiation, the bone marrow may reveal some degree of aplasia. In certain cases of chronic leucemia accompanied by anemia, it cannot be ascertained from the peripheral blood counts whether the anemia is due to replacement of the bone marrow by immature cells or whether the bone marrow itself is aplastic. In these instances, bone marrow study will determine whether radiation therapy is indicated. In acute leucemia, the bone marrow is invariably replaced by leucemic cells. In most instances bone marrow examination will differentiate between disseminated neuroblastoma, lymphosarcoma, multiple myeloma, agnogenic myeloid metaplasia, pernicious anemia, and aplastic anemia. It must be emphasized that the interpretation of differential counts from the bone marrow using supravital staining technique requires the long experience of a well-qualified hematologist, bone marrow biopsy may be very difficult of interpretation particularly if it is poorly prepared.

The removal of a node for diagnosis may be helpful in leucemia. Nodes are enlarged in all types of leucemia and on section are homogeneous grayish-white in appearance. Microscopically a node may show complete obliteration of its structure by leucemic cells, with invasion of the capsule by cells in the pericapsular tissue. It is impossible to differentiate the small-cell type of lymphosarcoma from lymphogenous leucemia. In myelogenous leucemia, individual cells are derived from the myeloid series and there are often large numbers of immature cells present. Eosinophilic myelocytes are particularly prominent. It is not uncommon for the leucemic infiltration to be present between the germinal follicles, although in some instances the latter may be erased.

**Differential Diagnosis**—A variety of pathologic conditions may be mistaken for leucemia just as leucemia may be mistaken for some other condition. Lymphosarcoma, particularly in children, sometimes sends into the circulation a large number of neoplastic cells, simulating acute lymphogenous leucemia. It has been suggested that this occurs when the lymphosarcoma has invaded a movable organ such as the lung (Isaacs). This condition has been labeled *leucosarcoma* (Steinberg, 1908). Leucosarcoma can be diagnosed by supravital staining. Wiseman (1936) has described in detail the means of discrimination, with the help of supravital staining, between two morphologically distinct types of lymphocytes which may be found in the circulating blood, one characteristic of leucemia and the other a circulating lymphosarcomatous cell. The lymphosarcoma cell ranges from 8 to 13 microns, being similar in size to the normal intermediate lymphocyte. The cytoplasm consists of a narrow rim about the nucleus with a moderate sprinkling of dustlike mitochondria and containing from

A normal or subnormal number of circulating leucocytes may be found in leucemia, although this is most common in the acute forms, it is also observed in the chronic forms of the disease. These are sometimes given the contradictory title of *aleucemic leucemia* but are probably best designated subleucemic leucemia. Actually, many cases of leucemia pass through a stage of development during which there is no leucocytosis, and it is then that this diagnosis is usually made. Very rarely, however, except perhaps in some acute cases, do the number of circulating leucocytes remain normal or subnormal throughout the entire course of the disease. Here, again, the important factor is not the leucocytosis but the presence of immature cells.

It should be emphasized that special staining techniques are of value for making the diagnosis of leucemia and differentiating the various types. Supravital staining, according to the method of Sabin, permits the study of living blood cells and is helpful for fine hematologic differentiation. This procedure used in conjunction with the Romanowsky stains, is sometimes of considerable value in determining cell identity. It aids particularly in the identification of the monocyte. It is also particularly useful in differentiating true leucemic cells from circulating lymphosarcomatous cells (leucosarcoma). The peroxidase stain is of practical value only in relatively rare instances. The details of the hematologic techniques which are useful in the leucemias can be found in the excellent monographs and textbooks of Forkner, Wintrobe, Blackfan, and Diamond.

**Anemia**—In the early stages of the chronic forms of leucemia, the erythrocyte count and the hemoglobin may be within normal limits, the majority of cases are accompanied by a more or less marked anemia. In chronic lymphogenous leucemia, anemia usually develops only terminally. At times the anemia may be hemolytic; anemia is characteristically severe with acute leucemias in which it is invariably normocytic. The anemia may be more severe than can be explained by the degree of bone marrow replacement, but this may possibly be explained also on the basis of toxemia (Haden).

**Thrombocytopenia**—A diminution in the number of platelets is not constant in chronic leucemia. It is more frequent in chronic myelogenous leucemia. In the later stages of the disease, however, a thrombocytopenia is present in most cases. In acute leucemias this thrombocytopenia is almost a constant finding and the number of blood platelets is usually reduced to below 100,000 per cubic millimeter, the bleeding time is prolonged.

**Basal Metabolism**—The basal metabolic rate is elevated in most patients with leucemia, this is more constant in the chronic myelogenous variety and seems to appear at a later stage of the chronic lymphogenous leucemia. In acute leucemia the basal metabolic rate is always markedly increased. Middleton, in a careful analysis of a group of cases, feels that there is a rough parallel between the basal metabolic rate, the leucocyte count, the number of immature cells, and the clinical condition of the patient. In his opinion, this parallelism is more constant in chronic lymphogenous leucemia.

**Biopsy**—A *bone marrow biopsy* is frequently valuable for making a definite diagnosis, particularly in subleucemic leucemia. Aspiration of bone marrow



ever, reveals aplasia of the normal cellular elements often accompanied by fibrosis. At autopsy, zones of extramedullary hemopoiesis may be found in the spleen, liver, and lymph nodes. Other pathologic entities can give a similar peripheral blood picture and the bone marrow can be replaced by amyloid, metastatic carcinoma, multiple myeloma, Gaucher's disease (Mettier).

*Agranulocytic angina* may present leucopenia, tendency to hemorrhage, oral manifestations, and prostration, all of which may suggest a monocytic variety of acute leucemia. Agranulocytic angina, however, is more common in adults than in children, is not accompanied by severe anemia, and, although a leucocytosis may be present, immature cells are rarely seen. In addition, the *platelet count is usually increased* and the bone marrow biopsy does not show leucemic infiltration.

*Infectious mononucleosis* may be confused with lymphogenous leucemia because of its lymphadenopathy, leucocytosis, and enlarged spleen. This condition, however, is seldom accompanied by anemia and usually shows a positive sheep-cell agglutination test which is never positive in leucemia unless horse serum has been recently given. In addition, the histologic study of the lymph nodes shows characteristic pathologic changes (Hall), and examination of the bone marrow will not show evidence of leucemia.

In children, *neuroblastomas of the suprarenal gland* may metastasize to the orbit and produce a characteristic exophthalmus and ecchymosis of the eyelids (see Tumors of the Suprarenal Gland, page 787), such cases may be confused with cases of chloroma, particularly because of accompanying anemia and poor general condition. A variety of other conditions such as mycosis fungoides, Mikulicz' disease, and certain forms of tuberculosis and syphilis may be confused with leucemias, but this rarely occurs when the diagnosis relies on more information than a leucocyte count.

It must be pointed out that cases of acute lymphatic leucemia in children are frequently mistaken for aplastic anemia because of the normal or subnormal leucocyte count, the thrombocytopenia, marked anemia, usually slight generalized lymphadenopathy, and enlarged spleen. The reticulocyte count in leucemia in contrast to that in aplastic anemia may be elevated, but a sternal bone marrow puncture usually resolves the diagnosis. However, in acute leucemias in children, articular manifestations may be diagnosed as septic in nature or suggesting inflammatory rheumatism. Rheumatic heart disease may be simulated by the presence of hemic murmurs, fever, and articular pains. Also, oral manifestations of acute leucemia in children may be confused with Ludwig's angina, or diphtheria.

### Treatment

Although hygienic and supportive measures are generally accepted as of some value in the treatment of leucemia, the only treatment which actually relieves the patients and temporarily restores them to well-being is radiotherapy. Pusey in 1902, discovered the beneficial effect of radiations on the adenopathies of a case of lymphogenous leucemia and shortly afterward Senn reported a remarkable recovery in a patient with myelogenous leucemia after treatment of

one to one dozen vacuoles. The nucleus of this lymphosarcoma cell is vesicular and contains a fine weblike chromatin with a rather eccentric single large nucleolus. The nuclear membrane is indistinct so that not infrequently there is some difficulty in sharply delimiting the area occupied by the nucleus.

The following diagram illustrates the essential differentiation between the cell of leucosarcoma and that of lymphatic leucemia (Isaacs)

	LYMPHOSARCOMA CELL (LEUCOSARCOMA)	LYMPHATIC LEUCEMIA
Size	7.5 x 9 microns to 12 x 13.5	Same
Nucleolus	Eccentric single (uniformly stained)	Light blue hole
Nucleus	Oval, oblong kidney shaped	No chromatin, no rim
Motility	None	
Mitochondria	Dustlike	Small spheres
Vacuoles nucleus	Safral red (1-10 periphery)	None

Leucemia may be simulated by many conditions presenting leucocytosis which are designated as leucemoid reactions. Hill classifies these reactions into (1) bone marrow irritation or stimulation (physical, chemical, or allergic), (2) liberation leucocytosis (overwhelming demand by acute hemolysis, severe hemorrhage, septicemia, pernicious anemia in crisis), and (3) ectopic hemopoiesis. By far the largest number of these leucemoid reactions are of the so called bone marrow irritation type. Hill has pointed out that in these cases all myeloid elements are present (myelocytes, myeloblasts, erythroblasts, and megakaryocytes), but the immature cells show no abnormal lobulation or granulation. The total white count in these leucemoid reactions may be over 75,000 with rather prominent eosinophilia and basophilia. Miliary tuberculosis, overwhelming infections such as osteomyelitis, severe reactions to intravenous medications, metastatic carcinoma of bones, and pyogenic infections may all stimulate this type of reaction. Table LXXVI summarizes the differential character of leucemoid reactions and leucemias.

TABLE LXXVI. DIFFERENTIAL CHARACTER BETWEEN LEUCEMOID REACTIONS AND LEUCEMIA  
(After Hill, J. M., and Duncan, C. N. Am. J. M. Sc. 1941)

LEUCEMOID REACTIONS	TRUE LEUCEMIA
1 Immature as well as mature leucocytes show normal morphology	1 Leucocytes usually appear atypical, particularly immature ones
2 Myeloblasts may be present but usually are under 10 per cent	2 Myeloblasts may be numerous as high as 99+ per cent
3 Immature red cells (normoblasts and erythroblasts) often increased in proportion to leucocyte immaturity	3 Immature red cells rarely increased in proportion to leucocyte immaturity
4 Platelets usually normal or increased	4 Platelets decreased, often severely may be increased in chronic myelogenous form only
5 Anemia variable depending on clinical factors	5 Steadily progressing anemia becoming extreme

One of the most difficult problems of differential diagnosis between leucemoid reactions and leucemias is offered by *aplastic myeloid metaplasia*. Here there is an increase of the circulating leucocytes with immature cells and accompanying anemia and splenomegaly. In the peripheral blood nucleated red cells and normoblasts are often found. Study of the bone marrow how

in chronic leucemia. The radioactive phosphorus ( $P^{32}$ ) is deposited in those tissues which show the greatest infiltration of leucemic cells, that is, liver, spleen, kidneys, and bone marrow (Warren). Reinhard concluded that in the treatment of chronic lymphogenous leucemia the results of administration of radioactive phosphorus are equal but no better than those of roentgentherapy of the spleen. He felt that in chronic myelogenous leucemia this method of treatment was preferable. No evidence is available as yet to show that the administration of radioactive phosphorus is of greater value in prolonging the patient's life, but there is evidence that it is more hazardous. If an overdosage of radioactive phosphorus is administered, unfortunate effects comparable to those of excessive external irradiation will follow. Platt has summarized the untoward effects of radioactive phosphorus on various tissues.

Intermittent total body roentgentherapy remains, in our opinion, the preferable form of treatment. This, however, implies closer control, frequent hospitalizations, and numerous laboratory investigations. The preferable technique of treatment and the optimum intervals between applications are subject to decision in the individual instances.

Some cases of chronic leucemia, particularly of the lymphogenous variety, are probably best served during the earlier stages of the disease by periodic observations and abstention of treatment. It is difficult to establish any definite criteria as to when such cases should be treated. The same is true as to the indications for further treatment in a patient previously irradiated. In the past, too much emphasis has been put on the rise of the leucocyte count but, as has been pointed out, this alone is not a good index for treatment, for it may not accurately reflect the condition of the bone marrow or the activity of the disease. The leucocyte count should be taken into consideration along with the general condition of the patient, the presence or absence of symptoms, and the information given by the clinical examination. In general, the presence of fatigue and anorexia, loss of weight, and bone pain may be taken as indications that treatment is indicated, as well in the nontreated as in the previously treated patient. Uhlmann has suggested that the basal metabolic rate is the best means of determining when radiotherapy is indicated, but although it is true that the basal metabolic rate is at times a better single index than the leucocyte count, it should not be taken as an absolute formula. Variations in the basal metabolic rate should be only one factor used in deciding when to institute treatment. In the majority of cases, long intervals without treatment seem to be possible, but in chronic myelogenous leucemia, treatment is more frequently indicated. During the course of treatment, the study of the leucocyte count is advisable. However, the rapidity of decrease in the count is more important than the actual number of cells.

Merrill has suggested the routine investigation of kidney function in cases of leucemia which present a high leucocytosis and are treated by radiotherapy. The breakdown of the white cells and the increase in the uric acid can result in nephrolithiasis.

In patients with profound anemia due to bone marrow replacement or to prolonged effects of radiations, repeated transfusions may be indicated. Iron

the spleen and the epiphyseal regions of the long bones. Since then, radiotherapy has been used as a palliative measure in the treatment of leucemias. For a long time patients with leucemia were treated by roentgentherapy directed to the spleen or to the leucemic adenopathies. It had been admitted that roentgentherapy had an indirect effect through a leucotoxin, produced by radiations in the tissues or in the circulating blood and which resulted in a systemic effect (Helber). This conception has been almost universally abandoned. Radiation therapy has been shown to have no effect on normal leucocytes in vitro (Jolly) or in tissue cultures (Lacassagne). Nor has experimental work in rabbits shown evidence of destruction of normal leucocytes in the circulating blood (Benjamin). However, the great majority of the immature circulating leucocytes which characterize leucemia are radiolabile and a great number of them are destroyed in the circulation following irradiation. The main problem in leucemia is however, the hyperplasia of the leucopoietic tissues which is at the basis of the leucocytosis. Heinke in 1903, described in detail the effects of irradiation of the spleen. He noticed changes in the Malpighian bodies 25 hours after irradiation and the lymphocytes entirely disappeared after thirty six hours. A rapid regeneration followed with complete reparation within two weeks. The same is observed in the thymus lymph nodes, and intestinal follicles. Bone marrow changes are also noticeable three hours after irradiation. Following intense total body irradiation of rabbits Lacassagne described changes in the myeloblasts erythroblasts and megakaryocytes which within three days resulted in marked depopulation of the bone marrow. This experiment produced an immediate transitory leucopenia followed by a transitory leucocytosis and then by a progressive leucopenia with ultimate restoration in eight days. There was also marked thrombocytopenia but little effect on the number of circulating erythrocytes. This is explained because of the marked difference in the life span of leucocytes (probably two to fifteen days) and erythrocytes (twenty to one hundred fifty days) and because of the migration of the white cells to tissue which constantly subtracts a large number of leucocytes from the circulating blood.

There is general agreement as to the palliation afforded by local irradiation of the spleen and of the leucemic adenopathies but there is argument as to the ability of this form of treatment to prolong life. In 1927 Teschendorf and later Dale introduced a method of irradiation of the entire body in the treatment of leucemia. Total body irradiation seems to be a more logical approach to a disease which is systemic in its manifestations but this form of treatment is considerably more hazardous. In 1931 Heublein initiated a method of continuous irradiation of the entire body by means of a unit designed by Failla in which the patient was irradiated day and night in his hospital room at a rate of one roentgen per minute. The results of continuous irradiation by means of the Heublein unit did not show any prolongation of the patient's life (Craver 1940). This method has been abandoned.

Recently thorough studies have been made of the effect of the administration of radioactive phosphorus orally or intravenously to leucemic patients (Lawrence Warren Reinhard). This method has been used with some success

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therapy may also give good results when hypochromic anemia is present. In the presence of secondary infection, particularly of the oral cavity, administration of penicillin is usually of value. Patients with myelogenous leucemia must be cautioned against indiscriminate extraction of teeth. If a patient with leucemia has to have teeth extractions, prophylactic penicillin should be given because of the risk of infection.

It is generally agreed that radiotherapy is contraindicated in cases of acute leucemia. It would be more accurate to say that radiotherapy offers these patients little advantage and that the rapid course of the disease continues in spite of it, but definite palliation is derived in some cases.

### Prognosis

There is a marked variation in the duration of life of patients with chronic leucemia. In general, the longer the evolution of the disease before treatment has to be instituted, the better the prognosis. Patients with chronic lymphatic leucemia have been known to live as long as twenty five years (McGivran) but in general they survive only three or four years from the suspected onset of the disease. At least 10 per cent, however, live ten years or more (Jackson, 1940). Untreated patients with myelogenous leucemia live an average of three years (Minot). Infiltration of the retina or enlargement of the lymph nodes in myelogenous leucemia usually indicates a terminal stage. Bleeding tendencies, large numbers of immature leucocytes in the circulation, and thrombocytopenia have an equally ominous prognosis (Lucia).

There is no proof that radiation therapy or any other form of treatment has ever cured a patient with leucemia, but Minot estimated that in myelogenous leucemia the duration of efficient life of patients treated by irradiation was 30 per cent longer than in those not treated. Hoffman reached the same conclusion in a study of a group of eighty two patients with myelogenous leucemia in whom the average duration of life was three and one third years. Craver (1940), in reviewing the results of the continuous total body irradiation in the Heublein unit, found an average survival of two years after treatment in patients with chronic lymphogenous leucemia, 10 per cent surviving more than five years. In chronic myelogenous leucemia, the average survival after treatment was also two years, with a smaller percentage of patients living more than five years. From these figures there appears to be little doubt that in chronic leucemia efficient life is increased with therapy, although total duration remains essentially the same and no patient is ever cured. In perhaps a few instances moribund patients may have been brought back to a short period of active life. Acute leucemia has a hopeless prognosis, the usual duration of life being about ten weeks (Mills). In 113 cases of acute leucemia summarized by Warren, eighty four patients died within two months from the onset of symptoms.

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Individual cells within a tumor may present a widely different susceptibility to radiations. In tumors composed predominantly of radiovulnerable cells (lymphosarcoma, myeloma), the administration of a small dose of radiations results in immediate destruction of a great proportion of these cells and in grossly evident reduction in the size of the tumor, although a recurrence of growth may rapidly follow. In tumors composed of a variety of cells in different stages of differentiation (epidermoid carcinoma), even a large dose of radiations may not affect the most differentiated cells (horny layer), there may be no grossly ostensible effect for days or even weeks, yet the destruction of the germinal cells eventually results in complete disappearance of the tumor. In tumors composed mostly of cells which are not radiolabile (malignant melanoma, myosarcoma), the most intense irradiation may not produce any immediate or delayed effect. These examples illustrate that the *radiosensitivity* of a tumor depends primarily on the radiosensitivity of the cell of origin, that the gross reduction in the size of a tumor depends on the proportion of cells that are immediately affected by the irradiation, that the lack of immediate ostensible response does not necessarily indicate radioresistance, and that radiosensitivity is not synonymous with radiocurability, although the radiocurability of a tumor depends, above all, on its radiosensitivity.

A misunderstanding of the radiophysiology of tumors has resulted in a veritable semantic confusion in respect to radiosensitivity (Stewart, Warren). The number of mitotic figures or the proportion of undifferentiated cells may be indicative of the immediate response of a *radiosensitive malignant tumor*, but anaplasia and reproductive activity are not *a priori* signs of radiosensitivity in any or all malignant tumors. A marked degree of differentiation in an epidermoid carcinoma may imply a lesser degree of radiosensitivity, but no epidermoid carcinoma deserves the qualification of *radioresistant*, the qualification is still less fitting to a basal cell carcinoma simply because it may fail to disappear as rapidly as others.

The preliminary condition of radiocurability is radiosensitivity. Radioresistant or faintly radiosensitive malignant tumors are not radiocurable, since their destruction by means of radiations requires a dose so intense that it produces a diffuse extirpative effect which implies necrosis of surrounding structures. A relatively small dose of radiations may result in a rapidly noticeable effect in a lymphosarcoma of the tonsil, while it may not appreciably affect an epidermoid carcinoma in the same area, yet, all other conditions equal, *the total dose required for the sterilization of either tumor does not differ greatly*. Moreover, one type of tumor may be cured by administration of rather different amounts of radiations, depending on several variable factors, including the period of time over which the treatment is given. Thus, the total dose necessary to sterilize different tumors is certainly not an index of their radiosensitivity.

The establishment of a scale of the radiosensitivity of malignant tumors is the result of clinical observation. In order of decreasing radiosensitivity, we find malignant tumors arising from hemopoietic organs (lymphosarcoma, myeloma), Hodgkin's disease, lymphoepitheliomas of the upper air passages,

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seminomas and dysgerminomas, Ewing's sarcoma of the bone, basal cell carcinomas of the skin, epidermoid carcinomas arising by metaplasia from columnar epithelium, epidermoid carcinomas of the mucous membranes, mucocutaneous junctions, and of the skin, adenocarcinomas of the endometrium, breast, gastro intestinal system, and endocrine glands, soft tissue sarcomas, chondrosarcomas, neurogenic sarcomas, osteosarcomas, and, finally, malignant melanomas. Some of the latter tumors are truly radioresistant and probably should not be mentioned, but a small proportion of them may present unexpected radiosensitivity (fibrosarcoma and melanoma), one variety of liposarcoma is definitely radio sensitive and is even radiocurable, which is in complete disagreement with the general conception that the radiosensitivity of malignant tumors depends upon the radiosensitivity of their cell of origin. The preceding list is only a scale of average radiosensitivity in each group, individual tumors may show radio sensitivity in advance of or following their place in this rough outline. Rare tumors of varied radiosensitivity are purposely omitted.

It has been demonstrated that interference with the blood supply of a radiosensitive tissue diminishes its radiosensitivity (Jolly). It may be concluded that poor vascular supply is a factor which may conceivably interfere with the radiosensitivity of a tumor. Insufficiently or inadequately irradiated tumors become less responsive to a second series of treatments, this used to be attributed by early workers to *radio immunization* of the tumor cells (Regaud 1922). But whether the radiosensitivity of the tumor cells is actually altered or not, inadequate blood supply (resulting from edema, atrophy, previous surgical interventions, secondary infection, previous burns, previous irradiation) definitely lessens the radiocurability of an otherwise amenable tumor. In reality this is due to diminished resistance of surrounding tissues which become incapable of standing the amount of radiations necessary to the sterilization of the tumor.

The total sterilization of a tumor requires a minimum total dose of radiations capable of destroying all "germinal" cells within a tumor, and consequently discontinuing reproductivity of malignant cells. Radiocurable tumors are those in which the administration of such minimum dose is compatible with sufficient recovery of surrounding normal tissues to assure a *restitutio ad integrum*. This margin between the destruction of the tumor and the untoward effects on neighboring normal tissues decreases as the tumor becomes less radio sensitive, it becomes a negative quantity in nonradiocurable tumors for the quantity of radiations necessary for the tumor destruction is incompatible with the life of surrounding tissues and implies irreparable injury or death. If the required amount of radiations is delivered in a single treatment the margin of safety is very narrow. Regaud (1922, 1927) established the experimental evidence that it is impossible to sterilize the very radiosensitive tissue of the seminiferous tubules of the testicle by the administration of a single large dose of radiations, even when the dose is sufficient to produce irremediable damage to the surrounding structures. Conversely, it is very easy to sterilize permanently the testicle of the same animal by the administration of a smaller total dose fractionated and administered at equal intervals. Regaud insisted upon the

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biologic similarity between permanently growing tissue of the seminiferous tubules and malignant neoplasms. His experiment gave the *coup de grâce* to the then predominant method of single massive doses, the *Therapia Sterilisans Magna* of the German school (Wintz) and effected a turning point in the history of radiotherapy. Regaud concluded, however, that a protraction beyond twelve days constituted a definite error capable of producing radio-immunization of the tumor. Coutard (1929) noted the possibility and advisability of protraction to several weeks in the treatment of epidermoid carcinomas of the upper air passages and established the basis of the *protracted-fractional method* of treatment, now almost universally accepted. But while the protraction of the treatment does enlarge the margin of safety, it also enhances the necessity for strict clinical control of the patients.

### Indications for Radiotherapy in the Treatment of Cancer

Radiotherapy has definite primary indications in the treatment of cancer in preference to, or to the exclusion of, other forms of therapy. *Curative radiotherapy* as applied to cancer is a formidable procedure charged with definite risks. It is an all-or-none undertaking which well deserves being called *radical radiotherapy* at par in seriousness with the diastolic performances of surgery (Buschke) but differing in results by its conservative character.

The choice of patients with localized lesions to be submitted to radiotherapy requires serious appraisal of the radiosensitivity of the tumor in question, of the material possibility of distributing throughout the tumor area the minimum total amount of radiations capable of sterilizing the tumor, of the existence of a *margin of safety* assuring the continued viability of the surrounding tissues, and finally, serious estimation of whether other forms of treatment offer the same or a better result more expeditiously or with less risk.

In *highly radiosensitive tumors* such as lymphosarcoma, lymphoepithelioma, and transitional cell carcinoma of the upper air passages and in seminoma, myeloma and Ewing's sarcoma the opportune and adequate administration of radiations is the undisputed form of curative treatment.

In the *moderately radiosensitive tumors* such as basal-cell carcinoma of the skin and epidermoid carcinomas of the skin, mucous membranes, and mucocutaneous junctions, radiotherapy may be most effective, but the choice of treatment should take into consideration other concomitant circumstances besides favorable radiosensitivity. A small basal-cell carcinoma of the skin may promptly and effectively be treated by wide excision. Radiotherapy must make place for surgery in the treatment of early carcinoma of the bronchus, since adequate irradiation implies possible perforation and gangrene, epidermoid carcinoma arising on a burn scar cannot be given a sufficient amount of radiations without danger of necrosis of the atrophic tissues of the burned area, so that a wide excision and skin graft is often more effective. Surgical excision of an otherwise radiocurable carcinoma of the lower lip facilitates immediate surgical removal of any metastasis. Epidermoid carcinoma which invades bone does not become radioresistant or even less radiosensitive, in fact, epidermoid carcinomas of the maxillary antrum are curable by roentgentherapy in spite





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of extensive bone invasion and destruction (Regato), but the invasion of bone diminishes the *margin of safety* between destruction of the tumor and damage to the surrounding tissues, particularly as invasion carries the implication of secondary infection. Since in these cases the sterilization of the tumor by means of radiations may imply long and painful elimination of sequestra, a surgical removal of the diseased structures, when possible, may be less mutilating and more easily tolerated. Lymph node metastases from epidermoid carcinoma are no less radiosensitive than their primary lesions but more often than not they are multiple, spreading over a large area, so that the administration of an adequate amount of radiations through a single large field is seldom possible, thus, surgical dissection of these metastatic lesions is a preferable form of treatment. But when a dissection is impossible or when it implies marked deformity (facial paralysis in excision of preauricular nodes), radiotherapy may be attempted if there is reasonable assurance that the metastasis is confined to a small area capable of standing intensive irradiation.

Another group of moderately radiosensitive tumors, the adenocarcinomas, may or may not be radiocurable, depending on the site of origin. Adenocarcinoma of the cervix is as easily sterilized by radiations as epidermoid carcinoma in the same area. Adenocarcinoma of the endometrium can be cured by radiotherapy alone, but it is generally admitted that hysterectomy should follow irradiation whenever possible to assure a greater chance of permanent control. Adenocarcinoma of the breast can sometimes be controlled by radiations but always at the expense of extensive damage to the neighboring tissues, radiotherapy is not justified unless the lesion is inoperable. Adenocarcinomas of the gastrointestinal tract may present variable degrees of radiosensitivity but are not radiocurable, they are more logically treated by radical surgery which assures simultaneous treatment of the primary lesion and of the potential, often extensive, metastatic area. Adenocarcinomas of endocrine glands are not radiocurable as a rule, although occasional long remissions are effected by the use of radiations.

*Poorly radiosensitive or radioresistant tumors*, such as the soft tissue sarcomas, sarcomas of bone, and malignant melanomas, are not radiocurable.

In addition to the indications of radiotherapy as a curative form of treatment, there are definite indications of *palliative radiotherapy* in advanced or incurable forms of cancer. To conclude that a given tumor is inoperable, however is not to imply automatically that radiotherapy is indicated, nor are advanced lesions necessarily benefited by radiation therapy. Those who appear most incredulous at the possibilities of curative radiotherapy often demand from it true miracles when other forms of treatment appear impotent or have failed. A great deal of discredit has fallen upon radiotherapy by its systematic association with the hopeless. Flattering as it may be to the radiotherapist to be asked to employ his powerful means for the simple purpose of psychotherapy, he should ponder that "*the transitory psychological benefit in the hopeless case must be balanced against the psychological and eventual physical harm to the group in which the method has real benefits to offer*" (Lampe).

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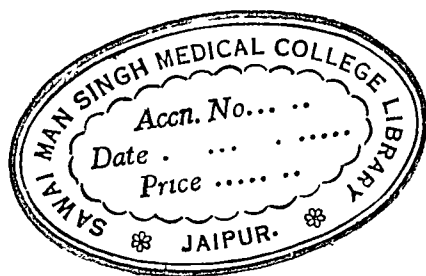
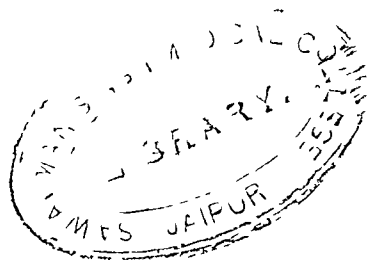
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*Palliative* radiotherapy may require serious advanced planning, an incomplete treatment or a few sporadic irradiations do not necessarily give relief. A variety of incurable conditions such as leucemia, Hodgkin's disease, recurrences or metastases of otherwise radiocurable tumors, recurrences or metastases of tumors which are tributaries of surgery may justify the use of radiotherapy as a palliative measure. In Hodgkin's disease and leucemia adequate radiotherapy results in unquestionable comfort and lengthening of life. In other instances, radiotherapy is applied locally to avert ulceration of a recurrent tumor and to avoid secondary infection or hemorrhage. Radiotherapy of metastatic lesions of the bone particularly of the head of the femur and of the vertebrae may avert fractures or paraplegias and contribute a transitory but definite analgesic effect. Apart from these and a few other instances, radiotherapy is not justified in the patient whose condition is hopeless.

**Pre- and Postoperative Irradiation**—The qualities that characterize the effectiveness of surgery and radiotherapy in the treatment of cancer can seldom be combined to produce an advantageous complementary effect. *Once inoperable, always inoperable* is a fairly current dogma among cancer surgeons which seems justified by the majority of facts. In some particular instances however such as in the treatment of adenocarcinoma of the endometrium the administration of preoperative radiotherapy brings about unquestionable improvement of the final results of surgery. In a restricted group of borderline inoperable lesions of the breast and gastrointestinal tract the administration of radiations results in diminution of secondary infection and inflammation and in a reduction of the size of the tumor which may thus become technically operable but this seldom contributes an improvement of the grievous prognosis of these lesions.

Following surgical intervention it may be that microscopic fragments of tumor have been left in the operative area or in the region of possible metastases but the postoperative administration of an amount of radiations sufficient to sterilize the tumor is seldom possible over such wide areas and anything short of this dosage is a futile attempt to remedy the irremediable. According to clinical experience, a thorough postoperative radiotherapy seems advisable in tumors of the ovary and in liposarcoma, whenever there is reasonable evidence that tumor has been left behind.

### Technical Aspects of Radiotherapy of Cancer

The *roentgen* is a unit of quantity of radiations measured through their ability to ionize air. In expressing doses of radiations in roentgens, it is pertinent to remember that the *dose delivered* (measured in air) is not the same thing as the *dose absorbed* (measured on the skin or in the tissues) that the ionization of air is not equivalent to the ionization of tissues and that the same amount of radiations absorbed may result in very variable effects in different tissues. The necessity for a biologic unit of radiations has been long recognized (Failla). On the basis of appreciation of the effect of radiations on the skin an *erythema dose* was established by Quimby, but there is a gross margin of error in the appreciation of the skin erythema and in fact, it may be argued



At best, the maximum total amount of radiations absorbed at any depth is always inferior (with 200 to 250 kv) to the amount absorbed and tolerated by the skin, and less than this amount is seldom sufficient to sterilize a malignant tumor. An increase in the amount of radiations absorbed in a given area can best be obtained by the utilization of several portals of entry and the *cross firing* of that area. The cross-firing of a tumor requires thorough knowledge of the actual extension of the tumor and of topographic anatomy (which is seldom possessed by unskilled personnel) to assure a thorough irradiation of the tumor area from every direction. This important part of radiotherapy cannot be underestimated, particularly as the fields of entry should be as small as possible to avoid untoward effects. For the delimitation of the fields, the use of metal "cones" is frequently unsatisfactory, and the use of additional lead

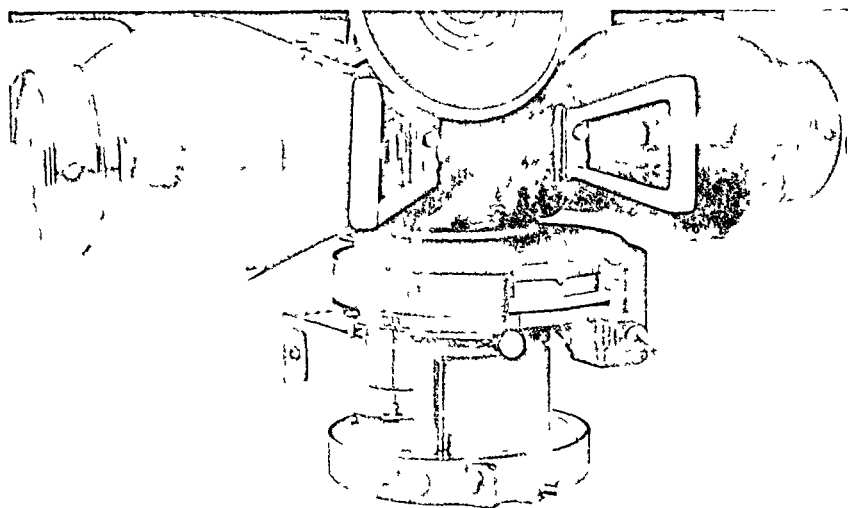


Fig. 22-1 The Lokuto localizer as it appears fixed to a tube-head. (Courtesy of I-R Machine Works, Long Island, N. Y.)

sheeting or lead rubber is often necessary. The device which has come to be known as the *Requato localizer* utilizes the physical reproduction of the beam of rays by a beam of light and facilitates the use of rectangular fields of all shapes by means of a diaphragm of easy maneuver and also circular fields of different diameters (Figs. 22-1 and 22-2), thus, fields of very small size can be used (latency) assuring the inclusion of the entire tumor.

The estimation of adequate doses is rather simple in the treatment of *superficial lesions*, since the optimum amount of radiations accomplishing the required aims is easily found by experience. In the treatment of deep seated tumors the estimation of dose requires evaluation from depth dose charts and curves of isodose. The appreciation of *tumor dose* is at best, a rough estimate, it is subject to error in evaluation of the tumor topography, since the actual

that the motor reaction of dermic vessels translates rather poorly the intensity of the more profound biologic effects of radiations on the epidermis (see Effects of Irradiation of the Skin, page 101). Since the effects of the same amounts of radiations delivered increase with the volume of tissue irradiated, a unit which would take this fact into account would be preferable to the simple expression of quantity of radiations delivered or absorbed. The idea of volume dose has resulted in the expression of the *mega gram roentgen* (Mayneord) and in a new concept of tolerance dose but has not as yet shown practical utility in clinical radiotherapy.

The expressions *lethal dose* and *cancer dose* have no basis in fact. The aim of radiotherapy is the administration to the entire tumor area of a total amount of radiations assuring the highest possibility of control of the tumor with the least chance of injury to the surrounding structures. In order to achieve these aims, the radiations must be as evenly distributed as possible, since the sterilization of the tumor depends on the absorption of the necessary *minimum* at all points while the viability of adjacent structures depends on the *maximum* absorbed at any point. The accomplishment of these requirements implies expert management of multiple technical factors.

**Roentgentherapy**—In the treatment of superficial lesions the distribution of the necessary dose throughout the tumor offers little difficulty. In order to avoid undesirable penetration of deep tissues, *low voltage* (80 to 100 kv) a *short target skin distance* (15 to 20 cm), and *no filter* or *weak filtration* (1 mm aluminum) are generally employed. In this manner the differential between the dose absorbed in the surface and that which is absorbed at any depth is greatly increased. Such treatments are generally of *short duration*. But if the lesion spreads over a large area or if it invades in depth or if it is near the eye, cartilaginous areas or bony surfaces then it is better to increase the quality of the beam and the margin of safety, by increasing the kilovoltage and filtration and further protracting the time of therapy.

In the treatment of deep seated tumors higher kilovoltage (200 to 250 kv) and a *maximum practical target skin distance* (60 to 100 cm) are chosen to assure less diffusion and consequently a larger transmission in depth (see Dispersion of Radiations, page 97), and the beam is *heavily filtered* (1 to 2 mm of copper). This results in an improvement of the relative proportion of short wave length radiations and in greater ability to penetrate while reducing the proportion of long wave length radiations and the undesirable effects of excessive back scatter. The amount and the quality of radiations received by a deep seated tumor however still depend greatly upon the secondary radiations created within the tissues (forward and back scatter) but an improvement in the *quality* of the incident beam does not result always in an increase of the *quantity* received in depth (Quimby). A problem not yet solved in dosimetry is the appreciation of *quality of radiations absorbed* at different depths in terms of the quality of the incident beam. An improvement in quality results in an increase in the margin of safety and consequently better quality may be desirable even when at the expense of the quantity.



greater radiosensitivity, or that better results would naturally follow the delivery of a greater quantity of radiations in depth and those who expected that the practice of radiotherapy would be thereby simplified. Such has not been the case. But because "supervoltage" roentgentherapy has a considerably reduced back scatter, there is a reduction of the volume dose and thus the cure of deep-seated tumors becomes possible with less injury or sequelae of the normal tissues than with the use of lower voltages. Moreover, the possibility of increasing slightly the depth dose in obese patients may be sufficient in many cases to attain the necessary minimum dose at the level of the tumor. The excellent results of "supervoltage" roentgentherapy in the hands of Cantrell and Buschke are more than a simple promise (see Treatment of Carcinoma of the Cervix, Bladder, and Esophagus).

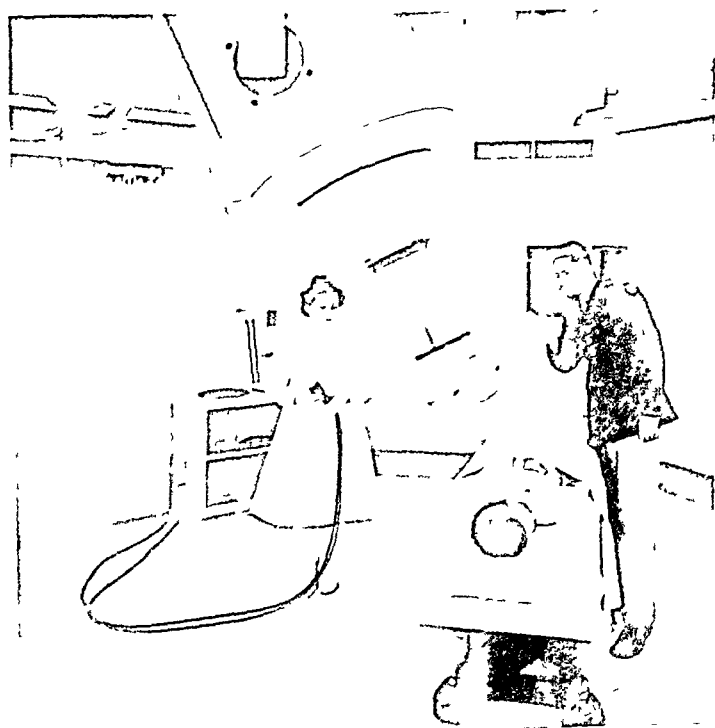


Fig. 23—One million volt radiotherapy apparatus, equipped with a lighting localizer to avoid use of hot  $\gamma$  cones. (Courtesy of General Electric X-Ray Corporation Chicago, Ill.)

**Curie therapy**—In the treatment of malignant tumors, radium is applied in different fashions which are important to distinguish. *Interstitial curie therapy* is the insertion of needles containing radium or of "seeds" containing radon (a radioactive gas emanating from radium) into the substance of the

extension of the tumor may not be known. It is subject to error in appreciation of the depth of the tumor from every point of attack, since human anatomy is variable. It is subject to the errors of the depth dose tables themselves which may differ from one another (according to Read, there is considerable difference between British and American values). It is also subject to error from direct adaptation of charts based on the "average" absorption of living tissues which do not apply to evaluation of depth dose in predominantly bony areas (lateral fields in the treatment of carcinoma of the cervix) or air filled organs

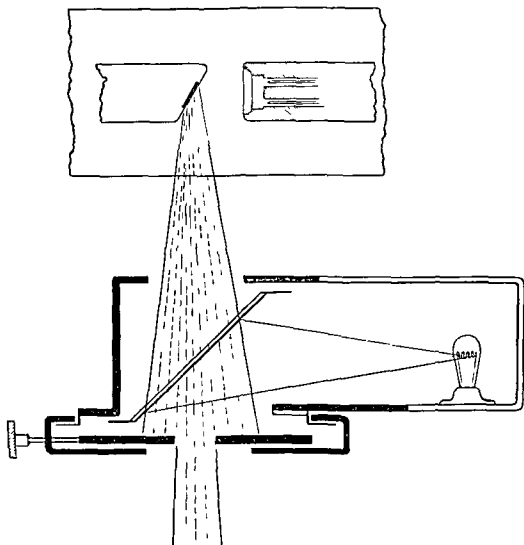


Fig. P—Schematic reproduction of the P-gato localizer. The beam of light reflected in the mirror superimposes itself on the beam of roentgen ray. A lead diaphragm facilitates the limitation of the beam into rectangular field.

Moreover the expression of tumor dose which is often advanced as the essence of accuracy is actually meaningless when not accompanied by an expression of the time of delivery, daily tumor dose, and other pertinent details. Nevertheless every effort should be made to establish the approximate tumor dose.

The advent of supervoltage roentgenotherapy has deceived those who expected that with the use of high voltage radiations tumors would present a

phosphorus ( $P^{32}$ ) with a short radioactive half life has been employed clinically in the treatment of generalized lymphosarcomas, Hodgkin's disease, leucemias, and polycythemia vera. There is unquestionable interest in the possibility of bringing radiations to all remote areas of the disease, but the amount of radiations necessary for the local sterilization of a malignant tumor however radio-sensitive is considerably greater than the amount which can be withstood by the hemopoietic organs, thus this method of treatment fails in its ultimate aim when applied to cancer. The careful use of radioactive phosphorus however, has yielded appreciable results in the treatment of chronic leucemias but its use in preference to other forms of radiotherapy has not been sufficiently corroborated. Its effects are unique in the treatment of polycythemia vera (Reinhard).

### The Clinical Control of Radiotherapy of Cancer

*The progress of Science results in gradual weakening of all primary concepts born of our ignorance the only strength of these concepts springs from the unknown and as that is dispelled quarrels must cease divergent doctrines must fade away and the scientific truth that replaces them must reign unruled*" (Bernard). Thus the development of our knowledge of the physics of radiations and of radiobiology and the progressive adaptation of this knowledge to the necessities of medical practice have resulted in progressive annihilation of empiricism in radiotherapy of cancer. But our limited scientific knowledge of radiations and their effects has not yet rendered simple or routine the daily practice of radiotherapy. Medical observation remains the basis of important decisions as to its conduct.

The strictly physical planning of radiotherapy leads, beyond certain limits to frequent failures and accidents. The radiotherapist who plans his treatments on physical charts and mathematical calculations to the exclusion of all other considerations is as dangerous as the most daring empiricist. It is Coutard's greatest contribution to radiotherapy that he demonstrated the primary importance of clinical observation and judgment in the conduct of treatments. Thus the radiotherapist has ceased being a technician whose knowledge and ability are confined to the use of his apparatus. Without underestimating the basic importance of a thorough knowledge of the physics of radiations the radiotherapist must also be thoroughly acquainted with the character of the disease he is attempting to treat and must be capable of observing the significant general and local reactions which occur in the course of treatments and of evaluating their importance. Above all the radiotherapist must be capable of reshaping his plans according to the clinical circumstances of the case rather than to follow preconceived formulas.

The clinical control of radiotherapy requires full evaluation of the case by the radiotherapist before treatments are started, secondhand information contributed or recorded is seldom satisfactory, for the information important to radiotherapy is not usually noted by other workers. In his preliminary acquaintance with any lesion the radiotherapist should evaluate the general condition of the patient, make a record of the symptoms and their intensity, appreciate the consistency and physical dimensions of the tumor as well as its topographic

tumor The value of this form of treatment relies on its ability to irradiate the tumor area intensely and yet without considerable effect on the surrounding structures With some exceptions (tongue, bladder) in which the placement of the sources of radiations can be accurately controlled, interstitial curietherapy often fails to administer a homogeneous irradiation to the tumor area *Intracavitary curietherapy* is the introduction of radium into natural cavities, the best example being in the treatment of carcinoma of the cervix *Surface curietherapy* is the application of radium on a molded apparatus with the purpose of increasing depth dose, in general, the radioactive sources are only 1 or 2 cm away from the surface of the tumor Finally, *telecurietherapy* is the use of relatively large amounts of radium at a greater distance from the tumor (10 to 12 cm) in the treatment of deep seated malignant neoplasms (also called radium "bomb" therapy)

An accurate dosimetry is not possible with the use of radium The dose expressed in *milligram hours* or *millicuries destroyed* is dose emitted, while the doses actually absorbed vary considerably, depending on the manner of application Curves of absorption for individual sources and for sets of applicators, with a definite relative arrangement of the sources, have been the subject of a very laudable study by Paterson and Parker The advent of the *roentgen* as a unit of quantity of radiations has naturally made evident the desirability of expressing radium energy in the same units, but this presents great technical difficulties A *gamma roentgen* has been defined to which milligram hours can be translated under certain specified circumstances, but the mistake should not be made of adding roentgens and gamma roentgens to express the accurate tumor dose—nothing could be so inaccurate

Radium has lost a great deal of its former indications in the treatment of cancer due to the steady progress in equipment and technique of roentgen therapy The hopes that were once put in telecurietherapy have now vanished But radium, in its demoted position remains nevertheless an indispensable part of the armamentarium of a cancer center

The introduction into the circulation of suspensions or solutions of radioactive materials was recognized long ago as an interesting subject of study (Aschmann 1903) and a possible therapeutic approach of systemic or generalized conditions The experimental injection of radium salts revealed that they rapidly concentrated in the liver lungs kidneys spleen, and pancreas, while no appreciable amount seemed to remain in the brain (Gies Burton Opitz and Meyer) The slow elimination of the radioactive material was done mostly in the urine and bile (Salant) but also in the saliva and tears and through the skin The injection of solutions of *radon* is followed by a more rapid elimination (Engelmann) but its products of disintegration accumulate in the bone, bone marrow spleen and liver (Inoué), Frangulla used the injection of radon for the treatment of generalized malignant neoplasms. Iacassagne (1925) experimented with polonium and concluded that the elimination of radioactive substances is handicapped by their injury to the organs of elimination and that an important fraction is retained in the reticuloendothelial system Similar experiments have been done with other radioactive elements Artificially radioactivated

this means that in the treatment of these carcinomas, the development of a radioepithelitis of the mucosa around the tumor area can be taken for a good sign of sufficient dosage

The *total dose* necessary to the sterilization of a tumor is established by experience. The same total dose may seldom produce comparable effects not only because the physical factors of its administration may vary, but also because in the adaptation of the daily delivery to the requirements of the case, the treatments end in different fractionations and protraction. The total amount of radiations which may be given to a tissue or region varies with the multiplicity of physical factors and also with the rate of delivery and personal susceptibility: only the experience of the radiotherapist can be of value in estimating the proper limits of dosage compatible with viability.

But while clinical observation and experience are of great importance in the conduct of radiotherapy, the radiotherapist cannot limit himself to be a clinical observer any more than he can conduct his treatments on the basis of physical knowledge alone. *"All sciences touch art at some point, all arts have their scientific aspect: the worst scientist is the one who is never an artist, the worst artist is the one who is never a scientist"* (Trousseau)

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spread and depth, other factors such as secondary infection, inflammation, edema collateral circulation, etc. must also be carefully recorded. In the course of treatments, the improvement or further deterioration of the general condition, loss or gain in weight, the persistence or disappearance of symptoms or the onset of new ones in addition to the changes of the tumor itself, become the factors on which the proper evaluation of the therapy is based, in addition, the systemic and local reactions due to the administration of radiations require daily evaluation. It is on the basis of these considerations that the final character of the treatment is shaped.

**Systemic Effects of Irradiations**—The indiscriminate administration of radiations results frequently in untoward systemic effects known as "irradiation sickness" which are exceptionally observed when treatments are intelligently conducted. These systemic effects consist in anorexia, nausea, vomiting, lassitude, pallor, lividity, profuse perspiration and even chills in extreme cases (Jenkinson). They are most often observed in women and are definitely associated though the mechanism is not understood with the irradiation of excessively large fields or with the use of excessive doses for moderate sized fields.

An infinite number of devices and medications have been advocated in the treatment of "irradiation sickness" any discussion of the relative merits of these treatments would weaken the basic argument that *the best way to deal with irradiation sickness is to avoid it entirely*.

In certain very radiosensitive tumors the *daily dose* is unimportant only the administration of a minimum total amount of radiations is necessary to assure local sterilization. In such cases the required fields are usually large but since a high daily dose is not necessary, the treatments need only be sufficiently protracted to accumulate the required total without general untoward effects or excessive local reactions. In tumors with a moderate radiosensitivity, however the administration of radiations below a certain daily minimum never results in control of the tumor even when the total amount administered may be brought to a maximum of tolerance. When tumors of this type are very limited in extent the daily dose may be raised at least during part of the treatments to relieve their destruction but when they are extensive, the battle is lost from the start since a high dosage is not compatible with the use of large fields.

**Local Effects of Irradiations**—The daily observation of patients in the course of radiotherapy may reveal signs which require immediate change in the character of the treatment (the daily dose, the size of the field, etc.) lest the too forceful application of radiations result in an early interference with the natural radiosensitivity of the tumor. Such is the case of edemas which may be observed in the very few days of treatment for a carcinoma of the larynx. The necessity for close control and repeated examinations is thereby explained. The regression of a tumor may reveal that its actual extension is greater than had been estimated requiring a revision of the size or position of portals. Contard developed the theory that in the treatment of carcinomas of the upper air passages the sterilization of the tumor could not be expected unless an epidermoidal effect was noted on the normal mucous membranes,

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# Part II

## Chapter VI

### CANCER OF THE SKIN

#### CARCINOMA OF THE SKIN

##### Anatomy

The skin is formed by several epithelial layers which compose the epidermis and by a dense underlying layer of connective tissue, the derma or corium. The basal layer of the epidermis consists of a palisade of somewhat columnar cells. Above the basal layer lie the stratum malpighii, the stratum granulosum, the stratum lueidum and, finally, the stratum corneum of desquamating, cornified cells.

The sweat glands, the sebaceous glands, and the follicles are found in the corium. The corium forms papillary projections into the epidermis, containing vessels and nerves.

**Lymphatics**—The skin of the forehead and temporal and malar regions is drained by preauricular lymph nodes. The skin of the lateral half of the eyelids and outer canthus is also drained by these nodes. A strip of the midline of the forehead, the medial half of the eyelids and inner canthus, the nose, lips, and cheeks are drained by submaxillary and cervical lymph nodes.

The anterior half of the skin of the ear is drained by the preauricular lymph nodes and its posterior half is drained by the upper cervical lymph nodes. The parietal and occipital regions of the scalp are also drained by the cervical lymph nodes.

The skin of the hand is drained by lymphatics which follow a long course to the epitrochlear and axillary lymph nodes. Many of these lymphatics go directly to the axilla.

The skin of the anterior and posterior chest walls is drained by the axillary and supraclavicular lymph nodes (Figs 99 and 100). The lymphatics of the lumbar region and anterior abdominal wall empty into the inguinal nodes. The lower extremities are almost entirely drained by lymphatics which empty into the inguinal lymph nodes, only a small area of the skin of the heel is drained by popliteal nodes.

##### Incidence and Etiology

Carcinoma of the skin is, without dispute, the most common form of cancer. This incidence is not apparent in mortality statistics because of its curability. The number of carcinomas of the skin seen in a given clinic depends greatly upon the proportion of out-of-door workers who are examined there. In our hospital, where mostly rural workers are seen, patients with carcinoma of the skin constitute 40 per cent of the total number of cases of cancer.

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much more frequently than persons with coarser or darker skin. A rare hereditary hypersensitivity of the skin to solar rays leads to a condition known as *xeroderma pigmentosum* and to multiple early carcinomas of the skin in children (Kaposi, Rouviere). It is well known that Arabs, South American Indians (Roffo), and Negroes (Hyde) are only slightly susceptible to the development of carcinoma of the skin. Schrek collected twenty cases of carcinoma of the skin in Negroes and found a comparable number in the skin of exposed and unexposed areas, and an equal distribution in both sexes. He concluded that chronic inflammatory lesions were more important than exposure to solar rays as a causative factor of carcinoma of the skin in Negroes.

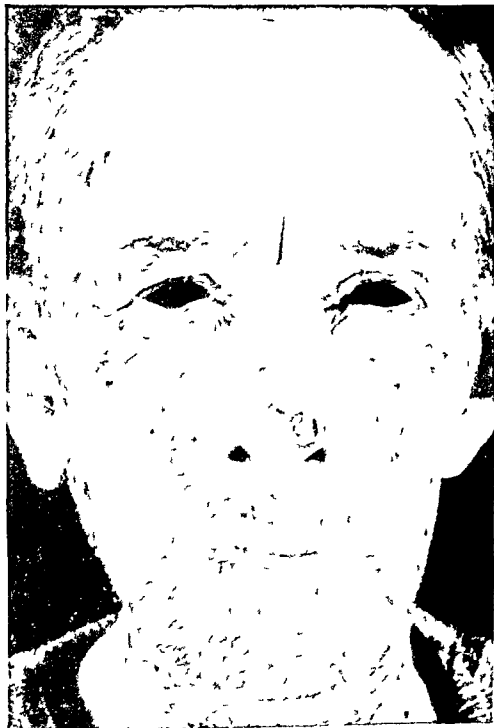


Fig. 26—Typical appearance of a farmer's face showing an almost normal skin of the forehead and multiple dyskeratotic changes of the skin of the nose, cheeks, and nasolabial folds.

Chronic exposure to solar rays may result in hyperpigmentation, but in individuals of ruddy complexion a transient erythema develops into a permanent hyperemia and telangiectasia of the skin of the exposed areas. In elderly farmers, the white pliable skin of the forehead, protected by a hat or cap, contrasts often with the smooth, shiny, red skin of the zygomatic, preauricular, and retroauricular regions and of the cheeks (Figs. 26 and 27). With time and further

Prolonged exposure to *solar rays* (over a period of many years) frequently results in the production of carcinoma on the exposed areas of the skin. This development is frequently observed in individuals occupied in out of door work such as farmers and sailors (Unna, Hyde). The excessive exposure of farmers during the busy summer months is complemented by the mild but continued exposure during the winter months when the sunshine is a natural and welcome calefactor during work. In fact, the average exposure to solar rays may be greater in the temperate areas than in the tropics, where the intensity of sunlight enforces the use of greater protection and a choice of the hours best suited for outside work. The chronicity of the exposure seems to be the most important single factor. Carcinoma of the skin seldom occurs in farmers before the age of 40 years, although they might have started continuous out of door work in childhood. In sailors, the intensity of the daily exposure to solar rays is reinforced by the reflection of sunlight on the water and its effects are perhaps enhanced by the salt and wind consequently, carcinoma of the skin is not infrequently observed in young sailors with a relatively shorter exposure than is found in farmers.

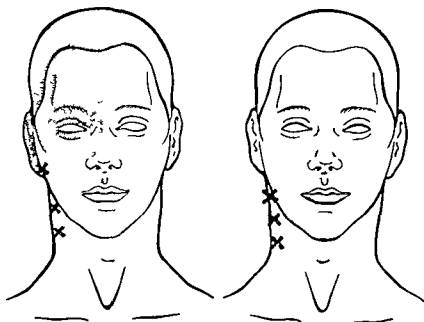


Fig. 4

Fig. 5

Fig. 4.—Metastases from epidermoid carcinomas of the skin are rare. Lesions of the temporal frontal and malar regions, the scalp and the outer canthus of the eye generally metastasize to the preauricular lymph nodes. Lesions of the cheek, inner canthus of the eye, nasolabial fold and nose may or may not metastasize to the preauricular nodes.

Fig. 5.—Epidermoid carcinomas which develop near the midline of the forehead, inner canthus of the eye, nose, nasolabial fold and cheeks may metastasize to the submaxillary or cervical lymph nodes.

There are definite racial differences in respect to the susceptibility to the development of carcinoma of the skin but these differences seem to be related simply to the texture of the skin and its pigment content. In general, persons with a ruddy complexion, such as average Scandinavians and North Germans seem to develop carcinomas of the skin after chronic exposure to solar rays.

an accidental overexposure, or following excessive unfiltered irradiation, or after large areas or areas close to bone have been irradiated, the low quality of the primary beam used or the excessive scattered radiations resulting in the field is the common denominator and probably bears the responsibility for the ultimate development of carcinoma. In general, however, the great number of



Fig 28.—Epidermoid carcinoma of the skin of the anterior abdominal wall with right inguinal metastases. This lesion developed on an area of skin which had received excessive amounts of radiations thirty-five years before.

cases of carcinoma of the skin reported as developing following therapeutic applications of radiation require close scrutiny. Many supposed carcinomas arising in the borders of an area of radioepidermitis, in a recently irradiated region, are of questionable identity. In excessively irradiated areas, a late radio-

exposure, definite patches of hyperkeratosis appear. Typical are the lesions of the skin of the ears and dorsum of the hands. After a variable interval, the hyperkeratosis gives place to the development of carcinoma. Carcinoma arises also from areas of the skin which although chronically exposed to solar rays have not been visibly altered.



Fig. 27.—Multiple dyskeratotic changes and multiple areas of early carcinoma on the skin of a man having worked all his life as a farmer. Notice the relatively good condition of the skin of the forehead.

Another important physical agent capable of producing carcinoma of the skin is the *roentgen ray*. Exposure to the primary beam of radiations or, more frequently, to scattered radiations reflected from objects hit by the primary beam, causes the development of a complex properly called *xeroderma pigmentosum roentgenologicum* (Hesse), the lesions frequently end in carcinomatous changes (Porter, Holthusen). Many worthy pioneers in the field of radiology paid with their lives for the knowledge which resulted in the present methods of protection. In addition to this occupational form of cancer due to roentgen rays, carcinomas of the skin also rarely develop upon irradiated areas (Fig. 28). In general, it takes many years after

reported seventeen cases of carcinoma of the skin developing in *nitrate* workers, most of these lesions developed on the hands and feet probably because of a carcinogenic agent contained in saltpeter plus added trauma. Tar and pitch have also been recognized as causative agents, but in many of the reported cases of pitch and tar carcinomas, the concomitant exposure to solar rays may have played an important role. Carcinomas developing on the skin of workers of oil refineries, mule spinners, machinists, metal lathe workers, etc., have been attributed to the carcinogenic activity of oils and paraffins (Hueper). The classical example of carcinoma of the scrotum of chimney sweepers due to soot is rarely seen today.



FIG. 20

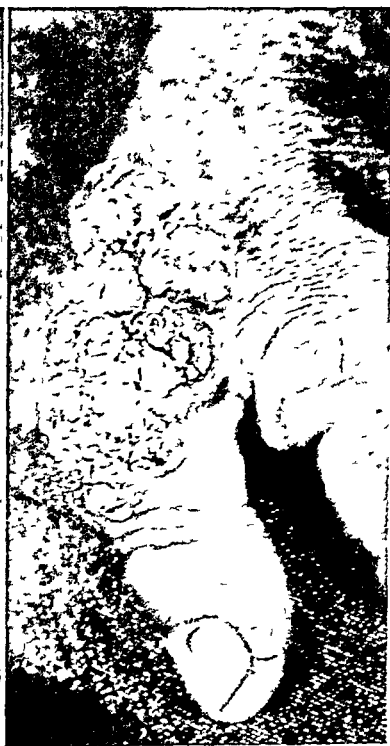


FIG. 21

Fig. 20—Epidermoid carcinoma of the skin of the dorsum of the index finger. Outside of the face, the dorsum of the hand is the most frequent location of a carcinoma arising on the basis of long-standing dyskeratotic changes.

Fig. 21—Verrucous carcinoma of the skin of the dorsum of the thumb.

The occurrence of carcinoma on burn scars is frequently observed (Lumière, Treves). As a general rule, carcinomas developing on scars of severe burns occur twenty to forty years after the accident, and arise usually from long-standing ulcerations. A peculiar form of carcinoma of the skin of the abdomen

dermatitis may result, and after many years a carcinoma may develop on this indolent ulcer. But here, carcinoma develops on atrophic, poorly vascularized tissue on a similar basis as it occurs in burn scars and probably without relationship to the cause of these changes. Finally, carcinoma of the skin arising after irradiation of lupic lesions is also questionable, since carcinoma may also arise from a lupus which has not been irradiated.



Fig. 9.—Large basal cell carcinoma of the lower part of the neck, an infrequent location.

Carcinomas of the skin may develop in relationship with certain chemical agents the most frequently incriminated being *arsenic*. The occurrence of a keratosis of the skin in individuals occupationally exposed to arsenicals or as a consequence of medicinal applications of arsenic has been widely observed, but the incidence of arsenical carcinomas is rather small in comparison with the widespread industrial and medicinal exposure to this agent. Characteristic of the carcinomas of the skin developing in patients who have received arsenical treatment is their frequent location in the palm of the hand, on the plantar region of the foot and in the inguinal regions. Montgomery and Waisman believe that these carcinomas are associated with a concentration of arsenic in the tissues and that they often begin as epidermoid carcinomas *in situ*. Guzman



and thighs is frequently observed in India among indigent Kashmiris, these carcinomas arise on the scars of burns caused by an earthenware bowl (*kangri*) which is filled with smoldering wood charcoal and worn under the garments as a portable calefactor (Ney)

Men are more frequently subject to carcinoma of the skin, perhaps because a greater number of them do outside work and because of differences in the chronicity of exposure. In carcinomas of the skin of unexposed areas (trunk and extremities), the proportion of males and females is usually comparable. The age of patients with carcinoma of the skin is variable, but except for xeroderma pigmentosum, carcinomas of the skin are very seldom observed in young individuals. In a review of 1,062 carcinomas of the skin of the face, de Cholnoky found only forty-five patients under 40 years of age. Eberhard, in a review of 492 cases of carcinoma of the skin, found a median age of 72 years.

### Pathology

**Gross Pathology**—Carcinomas of the skin are divided into two main types, the basal-cell carcinoma and the epidermoid carcinoma. The early basal-cell carcinoma usually has a gray, somewhat translucent, appearance and may be present as a small nodule beneath the thinned-out overlying epithelium. If the basal-cell carcinoma contains large amounts of mucin, it may have a cystic appearance and may even shell out of its bed. In the large basal-cell carcinomas, areas of yellowish necrosis are frequent. The epidermoid carcinoma, often keratinizing, may show yellowish-gray areas on cross section. The large epidermoid carcinoma with an ulcerated surface is heavily infected. The rare sweat gland carcinomas are frequently deeply invasive and at times cystic.

Carcinoma of the skin varies in its manner of growth. It develops outward to produce a bulge on the tumor, it may infiltrate and ulcerate the underlying tissues when it develops inwardly, or it may spread parallel to the surface of the skin, involving the epidermis alone or including the papillary layers (Stout). Both basal-cell carcinomas and epidermoid carcinomas may involve a wide zone with little infiltration in depth. As epidermoid carcinomas grow deeper, they often become fixed to underlying structures either because of inflammation or actual invasion. Epidermoid carcinoma of the dorsal surface of the hand is particularly prone to become fixed to underlying fascia, and it is impossible to determine grossly whether such fixation is inflammatory or neoplastic. The indolent, slowly growing basal-cell carcinoma may, over a period of years, destroy the entire side of the face, eat away the cartilage of the nose, destroy the bone of the antrum, and cause death through hemorrhage.

Both epidermoid carcinoma and basal-cell carcinoma, if treated inadequately, may heal over their surface and begin to spread in the deeper structures. This deep encroachment with spreading growth through many fine tendrils of tumor is often unappreciated by the surgeon, and exploration of a small previously treated basal-cell carcinoma may reveal a tumor with unexpected deep ramifications. The carcinomas of the sweat gland often recur locally and may invade underlying bone (Horn).



cells. Inflammation may accompany these tumors (plasma cells, lymphocytes, mononuclears) but usually this inflammatory exudate does not infiltrate the tumor proper. The individual cell of the basal cell carcinoma is characteristically spindle with oval nuclei, fine chromatin, and poorly defined cytoplasmic outlines. Mitoses are usually few in number. Melanin pigment may be found

Fig. 35



Fig. 36

Fig. 35—Bowen's disease of the skin. Note hyperplasia and intact basement membrane (low-power enlargement).

Fig. 36—Bowen's disease of the skin. The high-power enlargement reveals disorganization of the architecture, numerous mitotic figures, and foam cells (high-power enlargement).

**Microscopic Pathology**—The earliest microscopic changes of carcinoma of the skin are extremely difficult to evaluate. Such changes can occur in a single focus or in multiple areas (Wilks). The earliest change in a keratosis is often observed as an area of localized hyperplasia of the epithelium in which disorganization of the otherwise normal epithelium begins to occur. With these changes, increased mitotic activity, particularly in the basal layers, appears. In Bowen's disease, there is thickening of the epidermal layer, and the basal membrane remains intact (Figs 35 and 36). There are numerous foamy cells and mitotic figures, and monster cells with several nuclei are almost invariably observed (Bowen).



Fig. 34—Photomicrograph of a basal cell carcinoma, showing an excision with the limits of the tumor (very low power magnification).

The basal cell carcinoma arising from the basal layer of the epidermis has many different patterns, one variety of which often merges with another. Foot supports the concept that basal cell carcinomas arise from dermal adnexa rather than from the ordinary basal cell. He suggests that this tumor in its development, imitates the embryonal development of sebaceous and sudoriferous glands. These tumors can form keratinous strands show foci of keratinization, or may suggest hair follicles. Rather infrequently they are cystic with areas of mucin (Warren). Warren has divided the basal cell carcinomas into the simple basal cell carcinoma, the basal cell carcinoma with foci of keratinization, the epidermoid carcinoma (basosquamous carcinoma), cystic basal cell carcinoma (adenoides cystica), and hair matrix carcinoma. Most of these histologic types have little clinical significance. The desmoplastic basal cell carcinoma however, is important, for some of these tumors may recur. Multiple foci of origin of basal cell carcinomas appear, particularly in the superficial spreading type. The periphery of the tumor masses frequently have a palisade arrangement of cells.

## PLATE I

Epidermoid carcinoma of the ear

Extensive epidermoid carcinoma of the temporal and suprorbital region in a female

Extensive basal cell carcinoma of the skin of the nose

Epidermoid carcinoma of the skin of the forehead

Extensive basal cell carcinoma of the inner canthus of the right eye

Epidermoid carcinoma of the skin of the retroauricular region

Fig 3



Fig 38

Fig 37.—Early typical basal cell carcinoma of the skin (moderate enlargement)

Fig 38.—Basal cell carcinoma adenoides cystica with the typical cystic zones (very low power enlargement)



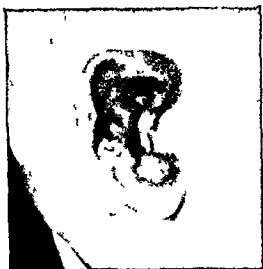


PLATE I



## PLATE II

Basal cell carcinoma of the outer canthus of the eye

Epidermoid carcinoma of the skin of the preauricular region

Typical slowly growing extensive nonulcerated lesion of the skin of the posterior chest wall (Bowen's disease)

Area of moist radiodermatitis showing peripheral and central regeneration of epithelium following palliative roentgentherapy for an advanced carcinoma of the breast

Basal cell carcinoma of the skin of the intergluteal space

Epidermoid carcinoma of the skin of the dorsum of the hand

of these, thirty two were females, while of thirty two patients with carcinoma of the skin of the ear (six basal cell carcinomas), only three were women

*Basal cell carcinomas* may or may not develop from a pre existing area of hyperkeratosis and they occur most frequently on the skin of the scalp, nose, nasolabial fold, eyelids, skin of upper and lower lips, chin, and forehead, they are rarely found on the anterior aspects of the ears, preauricular, temporal, and cervical regions, or dorsum of the hands. Typically, these lesions have a pearly appearance and are usually well circumscribed, in the larger ulcerated lesions, the pearly appearance is observed only in the rolled borders of the lesion. Their growth is slow and lesions having developed for years before medical consultation is sought are not infrequent. Basal cell carcinomas may be predominantly exophytic but a variety known as *rodent ulcer* is characterized by its destructive capacity and advanced lesions may destroy cartilage and bone extensively in their slow but tenacious growth (Fig 92). Still another variety of basal cell carcinoma may present a serpiginous superficial development, forming arcs of a circle around areas of normal skin, these lesions have been described as *flat cicatricial epitheliomas* because of their apparent spontaneous tendency to heal in places while developing further in other areas. They are also designated as *field fire type* of carcinoma.

When basal cell carcinomas arise on unexposed areas of the skin they usually originate from senile keratoses and are frequently multiple, nonulcerated, scaly lesions. Some treacherous lesions may continue their progressive destruction for years and the patients may die of hemorrhage or infectious complications.

*Epidermoid carcinomas* arise most often from pre existing patches of hyperkeratoses and occur predominantly on the skin of the cheeks, ears and preauricular, temporal and malar regions as well as on the dorsum of the hands. They are rarely found on the forehead, eyelids, nose, nasolabial folds, chin, or skin of the lips. The typical epidermoid carcinoma begins as a warty area, the keratotic surface may be removed and the bleeding base rapidly covers itself with a crust which requires larger proportions each time, finally, an ulceration develops which may be superficial but usually has indurated borders and a more or less marked secondary infection. The growth of an epidermoid carcinoma is more rapid than that of a basal cell carcinoma but the long history of pre existing keratoses seldom permits a proper evaluation of time of development. Epidermoid carcinomas are not necessarily excavating, some present an extensive outgrowth and only superficial ulceration but more often there is some degree of infiltration and fixation to deep structures, still others have a superficial spread or may present multicentric growths arising from neighboring areas of hyperkeratinization which finally become confluent. Invasion of fascia, muscles, cartilage and bone may take place. Local and referred pain is not infrequent due to secondary infection and the infiltrating properties of the tumor. Bleeding is not frequent but at times very severe hemorrhage occurs from exophytic as well as from ulcerating lesions.

Epidermoid carcinomas of the unexposed areas of the skin usually arise from burn scars, other scars or on chronic inflammatory lesions. Few epidermoid carcinomas of these areas arise from apparently normal skin.



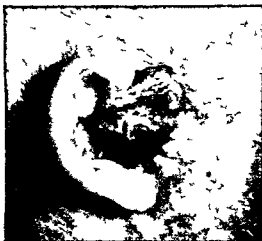


PLATE II

appearance of the lesion and its location, carcinomas developing from pre-existing keratoses are often epidermoid, although this is not always true. A knowledge of the time of development and history of previous treatments is of help in avoiding errors of diagnosis. Biopsy specimens should be removed from the clean borders of the ulcerated areas, should be deep, and should include some normal skin.



Fig. 40—Papilloma of the skin of the face suggesting a carcinoma



Fig. 41—Syphilitic lesion of the skin of the nose which was thought to be carcinoma

**Differential Diagnosis**—The existence of definite *precancerous dermatoses* is unquestionable. Hyperkeratoses of the skin of the face and hands, resulting from chronic exposure to solar rays, often become carcinomatous. The same is true of senile keratoses of the skin of the unexposed areas of the body and of

The proportion of carcinomas of the skin which metastasize to lymph nodes is very small. About one in every twenty epidermoid carcinomas of the skin of the face and neck metastasize to the preauricular, submaxillary, or cervical lymph nodes, carcinomas of the dorsum of the hand metastasize more frequently, about one in every five lesions metastasize to the epitrochlear or axillary lymph nodes, the proportion of metastases increases to about one in every three for epidermoid carcinomas of the lower extremities (Taylor).

Bowen, in 1912, described an atypical and proliferative "precancerous" lesion of the skin which later, at the suggestion of Darier, was called *Bowen's disease*. This lesion is pale red, slightly raised, and may acquire large dimensions. It usually appears on the unexposed areas of the skin, especially of the chest, although it is also rarely observed on the skin of the face. The growth is very slow (five to thirty five years), it seldom becomes ulcerated. Two or more such lesions may be observed simultaneously, although most cases present a single plaque. This characteristic clinical entity has been identified with certain histologic changes which are thought by many to be diagnostic (Stout). Unfortunately when a histologic criterion is chosen for the diagnosis, many other lesions of the skin and even of the mucous membrane which do not present a comparable clinical character become assimilated in this disease, the result is rather confusing. Montgomery believes that Bowen's disease is a veritable epidermoid carcinoma in situ, but this view is not accepted by others. Metastases are seldom observed from these lesions. To add to the confusion, basal cell carcinomas arising often simultaneously from the skin of the chest develop over periods of years and may present a comparable clinical appearance although their histopathology is quite different. In summary, Bowen's disease, undeniably a pathologic entity, is difficult to differentiate from other lesions by clinical and histopathologic criteria.

*Carcinomas of the sweat glands* are rare, they may originate from specialized sweat glands (apocrine, ciliary, and ceruminous) and are consequently observed around the anus, eyelids, and ears. They are also observed however, on the skin of the axilla (Fig 32) and scrotum. Their growth is slow, they tend to remain localized but may recur locally. Regional nodes are seldom implicated.

*Carcinomas of the sebaceous glands* are also rare and develop slowly, most often on the upper eyelids (Beach) but may also be found on the scalp, ear, forehead, nose, chin, chest, and scrotum. Beach and Severance reported six cases of metastases in seventy five patients with carcinoma of the sebaceous glands.

### Diagnosis

The diagnosis of carcinomas of the skin can be made clinically in the majority of cases, but a biopsy should always be taken to confirm this diagnosis. Ninety per cent of the cases, in a series of over 2 000 carcinomas of the skin, were accurately diagnosed clinically, while in over 1 000 lesions which were diagnosed clinically as benign, 15 per cent were found to be carcinoma on histologic examination (Torrey). The histologic variety of carcinoma can also be diagnosed with a high percentage of accuracy on the basis of the gross



Fig 43—Typical nodular tubercular tumor of long duration with innumerable lesions of the scalp

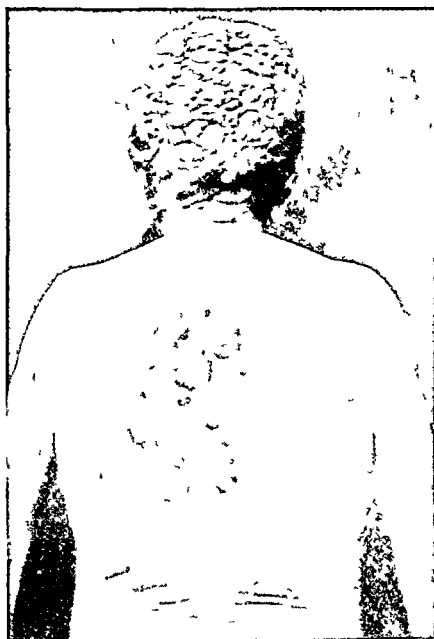


Fig 44—Same patient as in Fig 43 showing similar type lesions occurring on the posterior chest wall. This condition appeared in several members of the same family

**arsenical keratoses** Arsenical keratoses often appear in the palms and plantas and present clavuslike elevations. Montgomery estimates that about 20 per cent of these keratotic lesions may become carcinoma, their malignant potentialities should be considered rather than their benign appearance. Of ninety three lesions diagnosed clinically as keratotic, 37 per cent were actually found to be carcinoma (Torrey). A biopsy, and often repeated biopsies will be necessary to establish an accurate diagnosis. *Cornu cutaneum* is a keratotic malformation which needs to be treated with care since 5 to 10 per cent of them present epidermoid carcinoma at their base.

Lesions of *psoriasis* may be confused with multiple basal cell carcinomas of the skin of the chest, the typical occurrence of psoriasis on the skin of the elbows and knees may suffice to make the diagnosis, but biopsy may be necessary.



Fig. 42—Balign verrucous lesion of the skin of the face giving a clinical appearance of extensive carcinoma.

The serpiginous type of *tertiary syphilis* of the skin may reproduce the appearance of a superficially spreading basal cell carcinoma, the inflammatory type of syphilitic lesion of the skin of the nose (Fig. 41) may also be confused with carcinoma, the biopsy easily solves these problems of diagnosis.

*Nonpigmented nevi* may be confused clinically with basal cell carcinomas, this is also true of the *nonpigmented malignant melanoma* which may, in addition, be misdiagnosed histologically as a basal cell carcinoma. The lack of radiosensitivity of the lesion should betray the error in diagnosis.



epithelial lesion characterized by its multicentric development and slow growth. The individual lesions have a translucent grayish appearance (Ronchese), at times appear pearly, and may attain large dimensions (Figs 43 and 44).

*Glomus tumors* are rare, generally arising near the nail bed of the fingers and toes, but may also be found on the forearm and other parts of the body. They are characteristically painful and do not become ulcerated. The original description of these tumors was made by Masson. The glomus is a normal vascular anastomosis without intervening capillaries and includes special arrangement of muscle and nerve tissue. Murray and Stout identified the epithelioid cell of the glomus tumor as the pericyte of Zimmermann, thus offering an explanation for the occurrence of these tumors in parts of the body where glomus is not normally present.

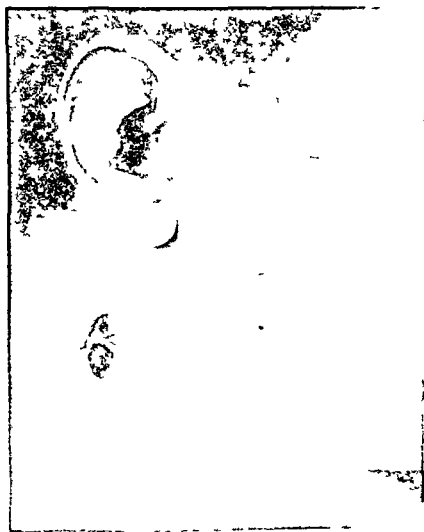


Fig. 46.—Lymphosarcoma of the skin of the neck in a young man. (Courtesy of Dr. F. Bacillesse, Department of Radiotherapy, Radium Institute of the University of Paris.)

*Kaposi's sarcoma* is a malignant lesion most often found on the skin of the lower extremities, usually occurs in men 50 to 70 years of age, and may develop slowly for many years. The individual lesions usually begin as red maculopapular manifestations under 1 cm. in diameter, which become darker, probably as a consequence of hemorrhage and disintegration of blood, and may also become cystic. Edema of the extremities often accompanies these lesions, and bleeding and secondary infection are frequent. The spread is in the form of new contiguous lesions which may be due to dermal spread. Metastases to lymph nodes and distant viscera may occur. Their histologic appearance is characteristic.

*Mycosis fungoides* is a malignant skin condition with the microscopic appearance of lymphosarcoma. It is easily confused with the skin manifestations

A sebaceous adenoma may resemble a basal cell carcinoma because of its pearly appearance, but it is usually softer (Nomland). Benign, verrucous, chronic inflammatory lesions of the skin may spread over large areas and appear as an extensive carcinoma (Fig 42).

*Pseudoepitheliomatous hyperplasia* is often confused microscopically with epidermoid carcinoma because of the deep penetration of the rete pegs and the apparent isolated nests of epidermal cells found deep in the biopsy. In this condition, polymorphonuclear leucocytes are often seen infiltrating the isolated islands of squamous epithelium. It does not usually occur in epidermoid carcinoma. The individual squamous cells are also well differentiated and naturally, if serial sections are made the deeply penetrating fingers of epithelium are seen to be continuous. This condition occurs in many chronic inflammatory lesions such as tuberculosis, syphilis, varicose ulcers and fungus infections of the skin (Winer).



Fig 43—Benign pigmented papillary nevi of the skin of the forehead

Lesions of *neurofibromatosis* (von Recklinghausen's disease) appear as multiple, nonnucleated, subcutaneous tumors of various dimensions, pigmentary disturbances (café au lait spots) may precede or accompany these nodular lesions. They have an easily recognizable histologic appearance.

A rare lesion of the skin of the forehead and scalp, variously referred to as endothelioma, cylindroma, or "turban tumor" may be confused clinically and histologically with basal cell carcinoma. The "turban tumor" is a benign

greater ease. A wide *electrocoagulation* of a skin carcinoma can also control the tumor but here, again, the necessity of assuring that all of the tumor has been destroyed implies large areas of destruction and consequent secondary infection and scarring, which even when justified are not as satisfactory as a wide surgical excision or adequate irradiation. Electrocoagulation as well as the application of escharotics can be done with a scientific understanding of the nature of the tumor and of the necessity of its total destruction, but more frequently these means because of their 'practical' aspects are used by unskilled practitioners and result in only partial destruction of the tumor and in deep diffuse recurrences (Ackerman), to make matters worse the destruction of a tumor by these means seldom contributes the necessary specimen for microscopic confirmation of the diagnosis.

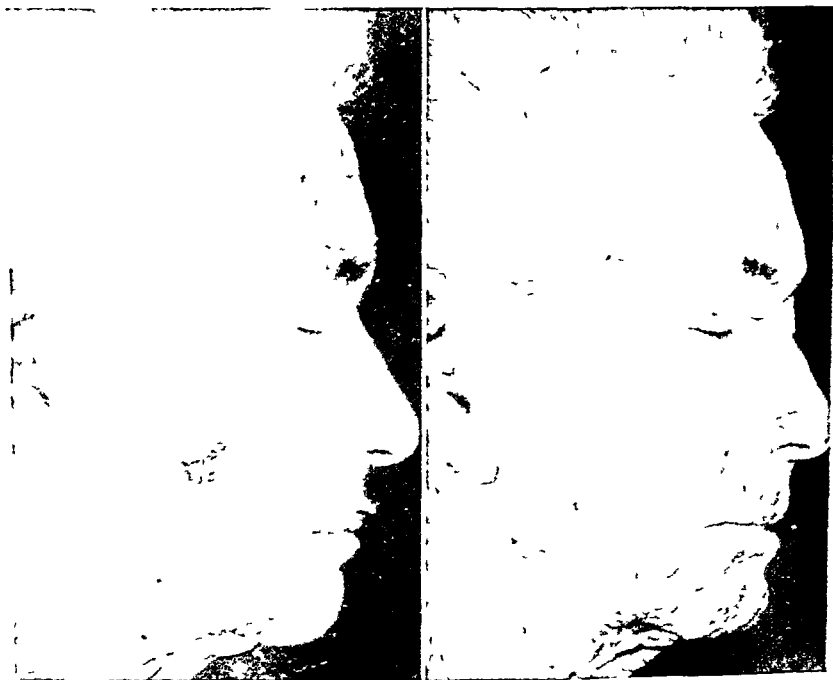


Fig 41

Fig 42

Fig 41—Basal-cell carcinoma of the chin of the cheek in a female presenting a cornu cutaneous of the upper lip and multiple dyskeratosis of the forehead.

Fig 42—Same patient after excision and skin graft.

The most common causes of failure in the treatment of carcinoma of the skin are (1) the administration of treatment by unskilled personnel without supervision (2) the systematic use of a single method or technique of treatment to cover all eventualities (3) the lack of histopathologic confirmation of clinical diagnoses and in the case of surgical excisions, lack of microscopic verification of the adequacy of the treatment, (4) the concept of primary healing as a

of leucemia and Hodgkin's disease, and for this reason its identity has been contested (Symmers). Mycosis fungoides develops in the form of raised skin plaques which pass through several periods of development over many years, extend over large areas of the body, and may become bright red or brown in color. An outstanding character is its failure to metastasize to lymph nodes or viscera. The lesions are very radiosensitive and locally curable, but development of new areas, repeated treatments, and infectious complications finally result in death. Survivals of fifteen to twenty years are common.

*Metastatic carcinoma* of the skin may occasionally be taken for a primary lesion, particularly when a solitary metastasis becomes ulcerated, but these cases are infrequent. Gates reported a collected series of 231 cases of metastatic carcinoma of the skin from lesions in the breast, stomach, ovary, uterus, kidney, etc. There was a solitary skin metastasis in only nine instances, and, although the metastatic lesion usually appears near the source of origin, it may be found very distant from the primary tumor.

### Treatment

Carcinomas of the skin are theoretically curable by a variety of therapeutic means, such as the application of escharotics, cryotherapy, electrocoagulation, cautery excisions, scalpel excisions, curettage, and roentgen therapy. In practice, however, the *injudicious* application of any of these methods is responsible for frequent failures which render incurable what originally was an innocent lesion.

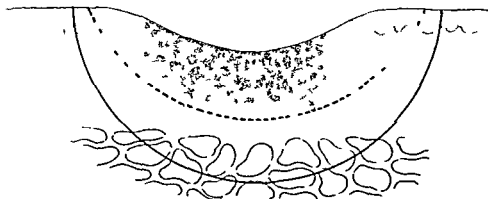


FIG. 4.—Small carcinoma of the skin are very often excised wide enough but not deep enough (dotted line). Pathologic examination should be directed to a certaining the complete removal of the tumor.

The local application of *nitric acid* or of a *zinc chlorid* paste results in fixation and necrosis of normal tissues as well as in the destruction of the carcinoma; however, the extent of the destruction, the secondary infection, and the pain which follows the procedure cannot be justified when more efficient means are available. Mohs raised the escharotics from their indiscriminate use by quacks to a scientific level. By painstaking, plane by plane, histopathologic control and by tracing the remaining areas to be treated, Mohs has succeeded in curing rather notable cases of carcinoma of the skin. His method requires especially trained technicians, absorbs time, and would be justified if other methods did not accomplish the same aims with greater certainty and with

tions or cosmetic repair. But whether surgery or radiotherapy is employed, it must be applied by experienced physicians who have a definite knowledge of the pathology of cancer.

**CURIETHERAPY**—Radium has been used successfully in the treatment of carcinoma of the skin, both in surface application and in interstitial application. The surface application of radium requires the time-consuming preparation of special molds and very careful planning of the treatment, but, at best, its

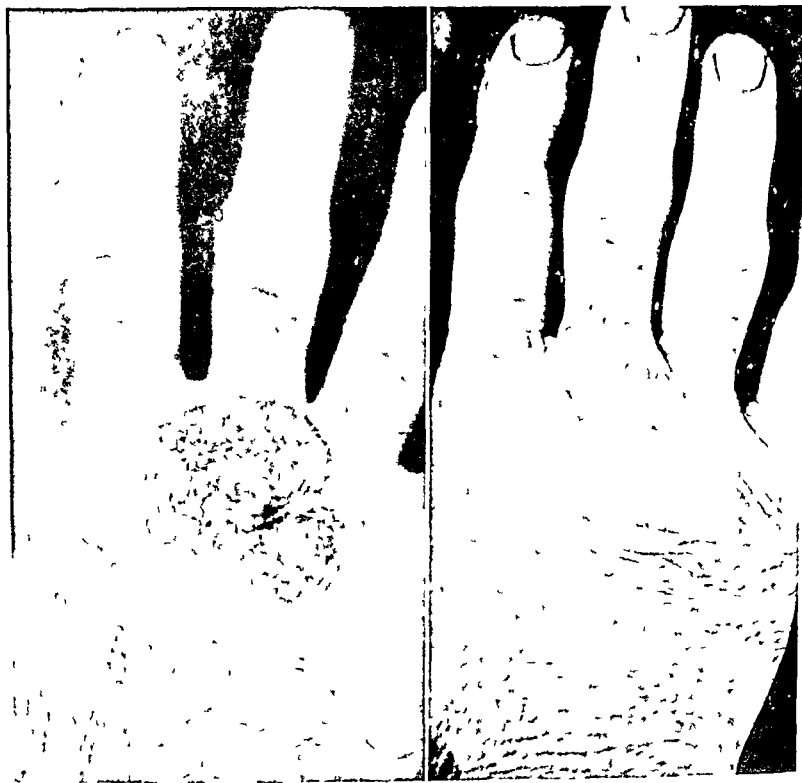


Fig. 52

Fig. 53

Fig. 52—Epidermoid carcinoma of the dorsum of the hand

Fig. 53—Same patient following excision and skin graft

results are not as satisfactory as those of adequate roentgentherapy in regard to the control of the disease and the cosmetic result. Interstitial curietherapy is an expeditious method of treatment which is only justified in small lesions. In these, however, a surgical excision is often more convenient. The interstitial application of radium carries the unquestionable danger of nonsterilization of the tumor due to uneven distribution of radiations and also the high possibility of late radionecrosis of the treated area.

criterion of cure, and (5) the self satisfaction emanating from lack of adequate follow up of patients. In this, as in other forms of cancer, the skill with which therapy is applied may be more important than the choice of method, but there is no special advantage attached to many of the methods which are used except that they do not require great skill. *The treatment of carcinoma of the skin may be reduced to the choice between its destruction by means of radiations or its eradication by means of surgical excision.* The choice of therapy depends mostly on the location of the tumor, its extension, and on the history of previous treatment. When the control of the disease can be accomplished with equal certainty by either radiotherapy or surgery preference may be given to the type of treatment which assures a better cosmetic result or to the one which can be accomplished with greater ease, but no such practical consideration

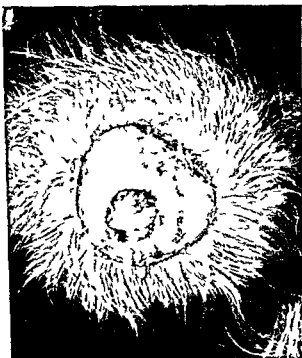


Fig 50

Fig 50 —Epidermoid carcinoma of the skin of the scalp arising on a sebaceous cyst.



Fig 51

Fig 51 —Same patient following excision and graft

should be entertained when the chances of control of the disease are hampered by the choice of method. Surgery will be chosen in some instances because its radical intervention offers the patient the best chances of permanent control of a carcinoma, in other instances, surgery will be favored only because of its expeditious character. Radiotherapy will be indicated because of its ability, when adequately applied, to destroy the carcinomatous tissue selectively without mutilation or dysfunction and with little or no visible sequelae, in other cases radiotherapy will be indicated because the extension of the lesion and its infiltration of deep structures make its treatment by any other method entirely impossible. In other instances, radiotherapy will only be chosen because it will accomplish with less difficulty what would require repeated surgical interven



Fig 56—Irradiation recurrence of a basal-cell carcinoma of the preauricular region following inadequate roentgentherapy for an advanced lesion



Fig 57



Fig 58

Fig 57—Same patient after wide excision and application of a tube pedicle graft.  
 Fig 58—Same patient after completion of plastic repair

**SURGERY**—A wide surgical excision is a very satisfactory form of treatment for carcinomas of the skin whenever the excision can be carried out without subsequent dysfunction or esthetic impairment. This applies to small lesions of the cheeks and cervical regions, where a surgical excision can accomplish without difficulty and in a single act the complete eradication of the tumor. Cautery excisions have no particular advantage, and, in fact, they modify the specimen, rendering its histologic study unsatisfactory. The adequacy of a surgical excision should always be verified by microscopic study of properly selected sections of the specimen (Figs 34 and 47). If tumor extends to the



Fig 54



Fig 55

Fig 54—Epidermoid carcinoma of the plantar surface of the foot in a Negro  
Fig 55—Same patient after excision and skin graft.

limits of the excision, the probability of recurrence is great and a wider excision of the diseased area or the administration of radiotherapy should be contemplated. In general, a margin of 0.5 cm beyond the apparent limits of the tumor is sufficiently safe for the excision of well delimited tumors. Unskilled surgeons usually remove a wide area around the surface of the tumor but fail to excise deeply enough frequently cutting through the deeper part of the tumor. Even in the case of an early, apparently harmless basal cell carcinoma such an error may lead to a diffusely infiltrating and deep recurrence with a lessened chance of cure. When the limits of the lesion are not well outlined



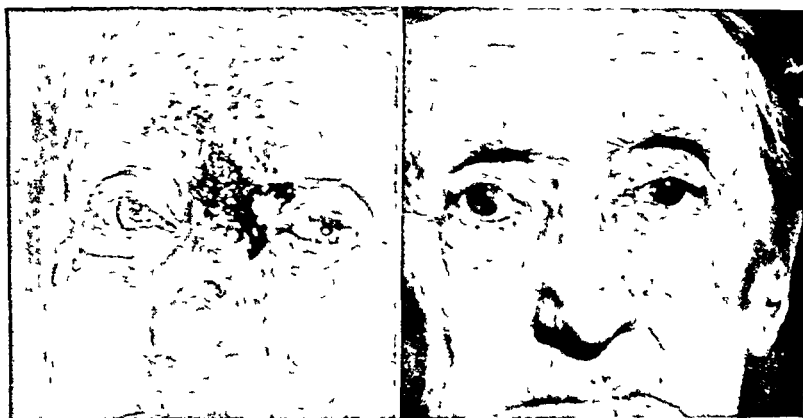


Fig. 63

Fig. 64

Fig. 63—Superficial basal-cell carcinoma of the skin of the bridge of the nose in an aged rural patient. Notice dyskeratotic changes of the skin of the forehead.

Fig. 64—Same patient four and one-half years following roentgentherapy.

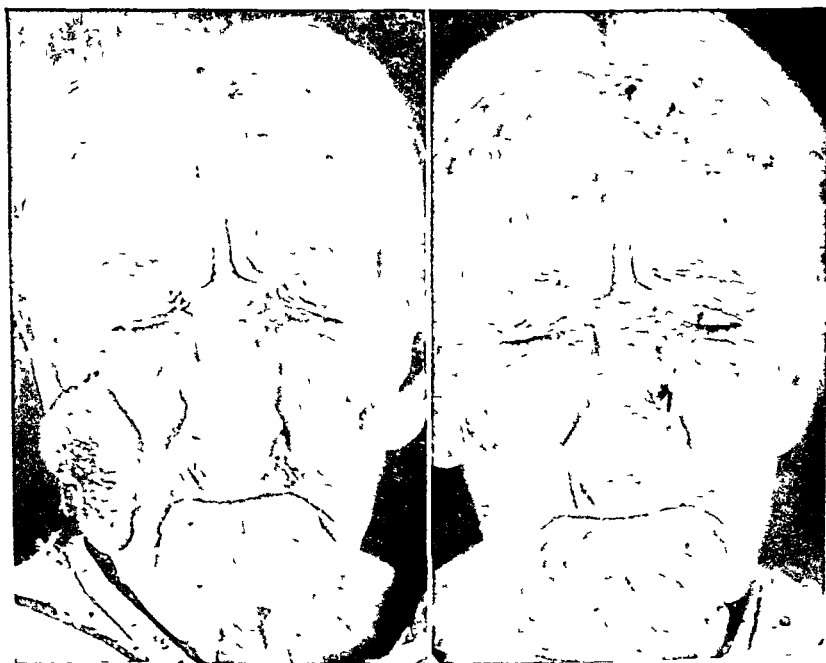


Fig. 65

Fig. 66

Fig. 65—Pedunculated epidermoid carcinoma of the skin of the right cheek. Note marked dyskeratotic changes of the forehead.

Fig. 66—Same patient four years following roentgentherapy. Other small carcinomas of the face were also treated.

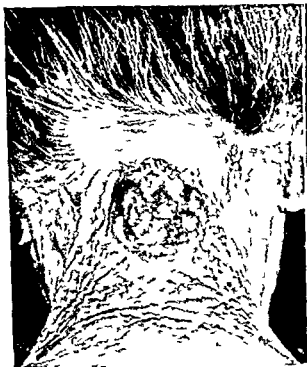


Fig 59



Fig 60

Fig 59—Extensive basal cell carcinomas of the skin of the nape of the neck  
 Fig 60—Same patient after wide excision



Fig 61



Fig 62

Fig 61—Basal-cell carcinoma of the skin of the forehead and frontotemporal region  
 Fig 62—Same patient following roentgen therapy

may imply mutilation or impairment of function. In such cases, preference should be given to roentgentherapy. This will, of necessity, be a laborious, protracted course of treatment which may achieve the conservative control of the disease and which does not interfere with a radical intervention in case of failure. Obviously, in more advanced cases of carcinoma of the skin of the hands, nothing but an amputation is logically indicated.

Surgery is also the treatment of choice for carcinomas of the skin of unexposed areas of the body. Often in these areas a large amount of tissue can be excised without inconvenience. Simple excisions, excisions followed by skin grafts, or amputations should be considered in cases of carcinoma of the lower extremities (Figs 54 and 55). In all tumors arising from scars or from lupus, the surgical treatment is the method of choice. Whenever a carcinoma of the sweat glands is suspected, preference should be given to its surgical removal. Finally, in cases in which inadequate irradiation has resulted in marked changes and in recurrence, a radical surgical excision, no matter how laborious or extensive, is the only hope of cure for the patient (Figs 56, 57, and 58).

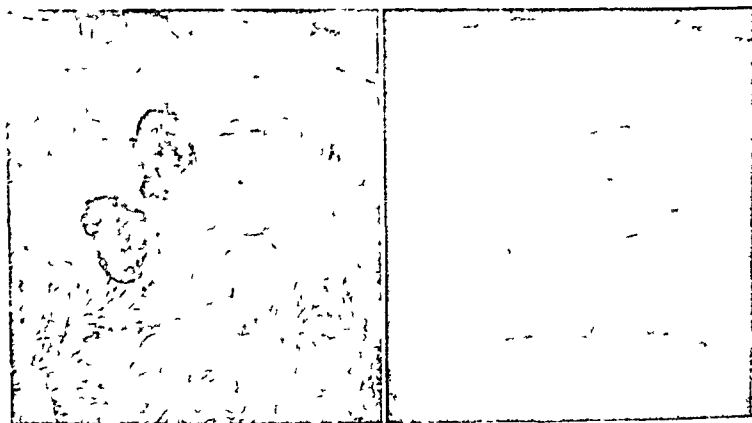


Fig. 69

Fig. 70

Fig. 69—Basal-cell carcinoma of the nasolabial fold and upper lip.

Fig. 70—Same patient three years after roentgentherapy.

In the treatment of metastatic carcinoma from primary lesions elsewhere, the radical dissection of the lymph nodes of the neck, axilla or inguinal regions is the logical therapeutic approach.

**ROENTGENTHERAPY**—Of all the forms of treatment of carcinoma of the skin, roentgentherapy is the one which has the widest range of indications and the greatest adaptability to the peculiarities of the given cases, but it also requires application with the greatest skill. Roentgentherapy is actually contraindicated in very few instances, such as in the treatment of carcinomas arising from scars. In most other instances where surgery is preferable, the choice is purely a practical one.

or when its extension is such that the resulting wound cannot be closed without deformity, a wide excision followed by skin graft is preferable (Figs 48 and 49) or radiotherapy rather than surgery should be administered. This is particularly important near the eyes, ears, and nose.

Fig. 67



Fig. 68

Fig. 67.—Basal cell carcinoma of the skin of the chin.

Fig. 68.—Same patient five years following roentgen therapy.

When a small carcinoma is surrounded by multiple hyperkeratotic lesions, a wide excision, including these potentially malignant lesions, followed by a skin graft may be the most satisfactory means of avoiding repeated treatments to neighboring areas. Superficial carcinomas of the skin of the scalp are adequately treated by excision and skin graft (Figs 50 and 51). Lesions of the dorsum of the hand which have not invaded in depth can also be very satisfactorily controlled by an excision and graft (Figs 52 and 53). The expeditious character of the procedure is an important factor here, but carcinomas of the dorsum of the hands may be adherent to tendons and their surgical treatment

the nose, and of extensive or diffusely infiltrating lesions elsewhere, the suppleness of roentgentherapy and its adaptability to the peculiar requirements of the lesion or of the region cannot be excelled by any other method (Regato)

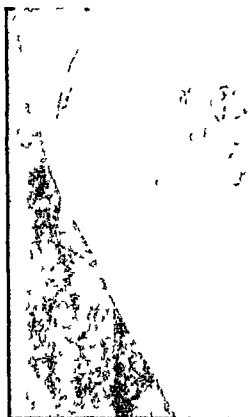


Fig. 70

Fig. 70—Basal cell carcinoma of the skin of the ala nasi having invaded and eroded the cartilage

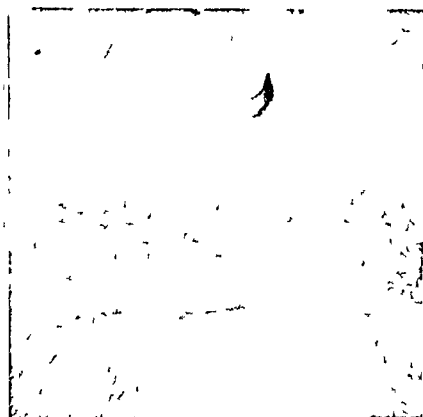


Fig. 71

Fig. 71—Same patient three years following roentgentherapy with perfect healing in spite of cartilage defect

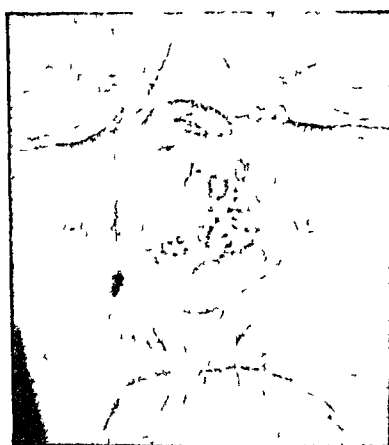


Fig. 75

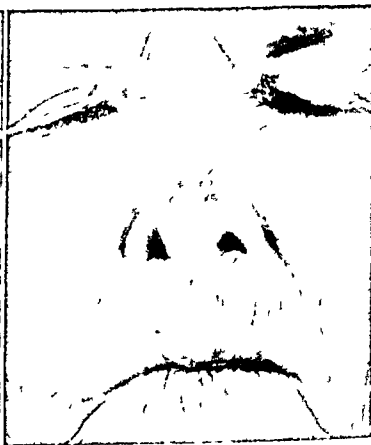


Fig. 76

Fig. 75—Extensive epidermoid carcinoma of the skin of the nose

Fig. 76—Same patient three years following roentgentherapy

The invasion of or the proximity of a tumor to cartilaginous or bony structures is not a contraindication to roentgentherapy but simply a circumstance requiring special adaptation of techniques (Figs 79 and 80) Single treatments

The success of roentgentherapy depends on its ability to achieve, as nearly as possible, the homogeneous distribution of a minimum amount of radiations, assuring complete destruction of the tumor, throughout the entire tumor area. Failures may result from insufficient irradiation or uneven distribution of radiations. In carcinomas arising in certain areas of the face, the aim of

Fig. 71



Fig. 72

Fig 71 —Epidermoid carcinoma of the skin of the temple

Fig 72 —Same patient following roentgentherapy

sterilization of the tumor is closely followed by the important consideration of preserving the normal structures and avoiding disfigurement. In the treatment of carcinomas of the eyelids, of the inner and outer canthus of the eyes, of the skin of the ears, of the preauricular and retroauricular regions, of the skin of

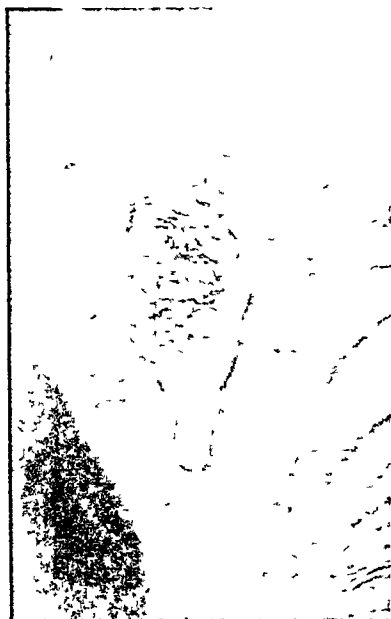


Fig. 51



Fig. 52

Fig. 51—Basal-cell carcinoma of the posterior aspect of the ear

Fig. 52—Same patient after roentgen therapy

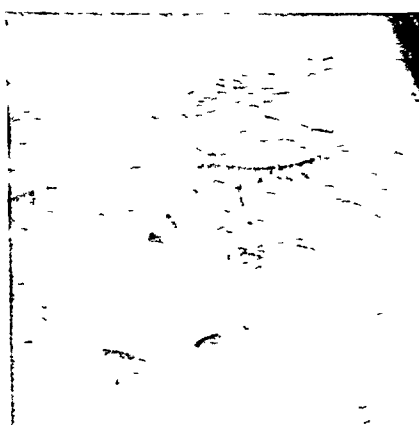


Fig. 53



Fig. 54

Fig. 53—Basal-cell carcinoma of the skin of the naso-orbital region

Fig. 54—Same patient following roentgen therapy

using unfiltered radiations can be applied with impunity in the treatment of small lesions or of those so situated that the resulting atrophy can be easily dissimulated. But such technique frequently leads to undesirable results when applied to carcinomas of the eyelids. Late radionecroses are frequent when such massive treatment is applied to skin lesions overlying bone such as in the preauricular and retroauricular regions. Painful chondronecrosis often follows



Fig. 7.

Fig. 8.

FIG. 7.—Basal cell carcinoma of the skin of the preauricular region with invasion into the concha of the ear.

FIG. 8.—Same patient three years after roentgen therapy.

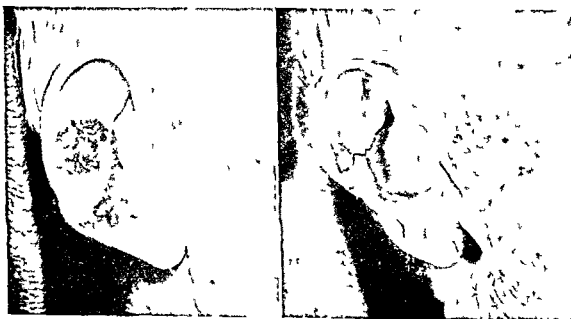


Fig. 9.

Fig. 10.

FIG. 9.—Epidermoid carcinoma of the skin of the anthelix spreading superficially and invading the cartilage.

FIG. 10.—Same patient following roentgen therapy with complete healing in spite of cartilage defect.



the rapid delivery of large amounts of low quality radiations, such practical aspect is far from compensating for the unequal distribution of radiations or excessive sequelae. The method accomplishes nothing that cannot be excelled with the adequate administration of conventional roentgentherapy. (Garciga)

Fig. 27

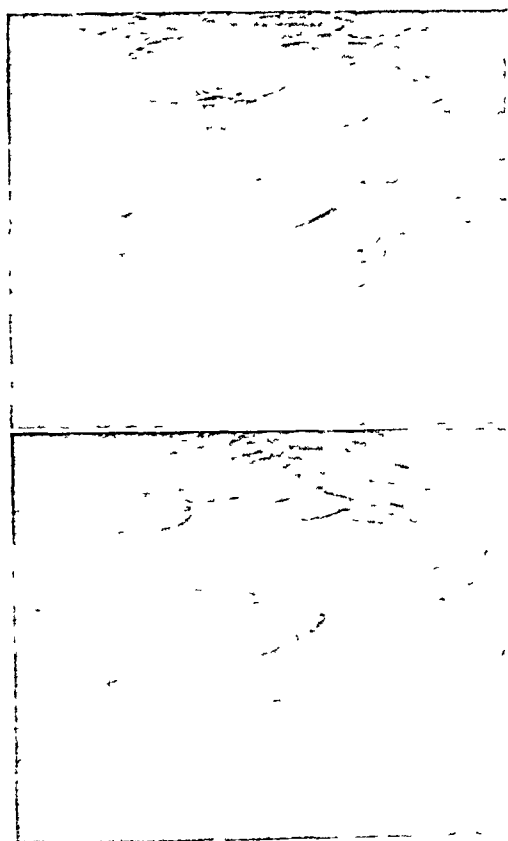


Fig. 28

Fig. 27—Focal basal-cell carcinoma of the skin of the lower eyelid and outer canthus.

Fig. 28—Same patient, after roentgentherapy. The only sequelae is an opacification of the outer third of the lower eyelid. There is no conjunctival or chronic inflammation of the eye and no evidence of adequate protection.

Basal-cell and epidermoid carcinomas of the skin show a different radiosensitivity but are equally radiocurable. No differences in dosage of radiations are warranted, and there is no greater chance of recurrence in either case provided the treatments are adequate. Recurrences following roentgentherapy can be ascribed and often traced back to a definite defect in the technique of

the application of unfiltered radiations to lesions of the nose and ears. On the contrary, well filtered radiations applied with convenient protraction eliminate these untoward effects while assuring the success of this conservative treatment (Merritt). The size of the lesion and its location will determine the quality of radiations needed, the maximum daily dose administered and the required protraction. The minimum total dose which is necessary to sterilize the tumor will

Fig. 8.



Fig. 9.

Fig. 8.—Basal-cell carcinoma of the inner canthus of the left eye.

Fig. 9.—Same patient 6 months after x-ray therapy.

vary with the size of the field, the quality of the radiations and the average daily dose (Heaton). The cosmetic result depends greatly upon the proper balance of these factors. This implies unquestionably a diversity of techniques to be applied to the circumstances of the case and it forbids the utilization of a convenient but irrational standard technique.

The treatment of cancer of the skin with special low voltage equipment of the Chroul type (contact therapy) offers no special advantage except for

measurable. In a large group of patients with carcinoma of the skin, the period of control may be reasonably limited to three years since recurrences are rare after that period. In presenting large statistics of results, most authors have been confronted with the problem of a large number of deaths due to intercurrent disease in groups of patients who, as a rule, are advanced in age. Patients who die of intercurrent disease within this period cannot be entirely eliminated in the computation of results for some could have developed recurrence of carcinoma. If these cases are included in the statistics and considered as failures the result is equally inaccurate. Magnusson computed his failure rate in the group of survivors and multiplied the number of deaths from intercurrent disease by this factor. Thus he found a hypothetical number of failures, which might have occurred in that group and added it to the known number of failures for the final computation. Calculated in this manner Magnusson found that the three-year survival rate in 571 patients with basal-cell carcinomas was 93 per cent and in 174 with epidermoid carcinomas it was 77 per cent.



Fig 91



Fig 92

Fig 91—Advanced basal-cell carcinoma of the skin of the cheek having invaded the nasal fossa, the maxillary antrum and the orbit.

Fig 92—Same patient following administration of roentgentherapy over a period of seven weeks. The patient remains well in spite of the excessive destruction produced by the tumor. Notice almost complete absence of sequelae due to the treatment.

From 1934 to 1938 1 033 patients with basal-cell carcinomas and 511 with epidermoid carcinomas were treated at The Holt Radium Institute of Manchester. The net five-year survival was 96 per cent for the basal cell and 80 per cent for the epidermoid. The overwhelming majority of the patients were treated with radium (Pateison). A group of 148 patients who died of intercurrent disease before five years was not included in the computation. About 65 per cent of the patients were over 60 years old.

From 1939 to 1942 367 patients with a total of 545 basal-cell carcinomas, plus 154 patients with a total of 197 epidermoid carcinomas, were treated at the Ellis Fischel State Cancer Hospital. Eberhard computed the results in these

treatment. No carcinoma of the skin can be called radioresistant. The reputed radioresistance of the adenoides cystica type of basal cell carcinoma is a myth.

In general, metastatic adenopathies from epidermoid carcinomas are more satisfactorily managed by radical surgical treatment, in the case of isolated preauricular metastases a thorough roentgentherapy may succeed in sterilizing the node without a facial paralysis and because of this its use may be considered



Fig. 89

Fig. 90

Fig. 89—Advanced basal cell carcinoma of the skin of the nose having invaded the cartilage and the facial bone.

Fig. 90—Same patient remaining well five years after roentgentherapy. (Courtesy of Dr. T. I. Oberhard, Jefferson Medical College, Philadelphia, Pa.)

### Prognosis

Carcinomas of the skin have the best prognosis of all malignant tumors which affect man. But, as it has been pointed out, this relative advantage is frequently wasted by the administration of inadequate treatment leading to incurability. Consequently, the greatest efforts should be made to assure adequate treatment even in the most incipient lesions.

Under ideal circumstances failures of treatment can be reduced to a negligible minimum and few untreated cases are seen which may be considered

the skin at the Royal Cancer Hospital of London of 174 patients with basal-cell carcinomas, 159 (91 per cent) survived three years, 59 patients (70 per cent) survived three years in a series of 84 cases of epidermoid carcinoma

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cases using the method of Magnusson and found that the three year survival rate was 87 per cent for the patients with basal cell carcinomas and 75 per cent for those with epidermoid carcinomas. Most of Eberhard's patients were treated by means of radiations, only a total of seventy seven lesions were treated surgically, the group had a mean age of 72 years and patients were not selected

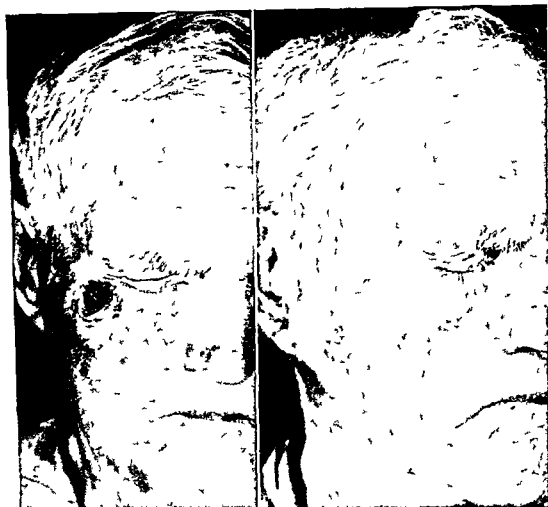


Fig 93

Fig 94

Fig 93 —Epidermoid carcinoma of the malar region

Fig 94 —Same patient following roentgentherapy for the primary lesion. A preauricular metastasis developed, proved by biopsy. The patient remains well and without facial paralysis three years after roentgentherapy to the lymphadenopathy

Statistics on smaller numbers of selected cases may show a still better proportion of good results. The site and the size of the lesion have a definite bearing on the prognosis but very advanced basal cell carcinomas which have received no previous therapy may still be controlled (Figs 91 and 92). The presence of a metastatic adenopathy darkens the prognosis of epidermoid carcinomas. Recurrences following inadequate excision or irradiation have the worst prognosis.

The comparison of results of different methods is often unfair due to the different choice of cases and the unequal skill with which treatments are applied. Smithers reported the results of roentgentherapy in carcinoma of

the skin at the Royal Cancer Hospital of London of 174 patients with basal-cell carcinomas, 159 (91 per cent) survived three years, 59 patients (70 per cent) survived three years in a series of 84 cases of epidermoid carcinoma

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## MALIGNANT MELANOMAS OF THE SKIN

### Incidence and Etiology

Under the term melanomas there are a group of skin growths which contain melanin pigment and which appear on the skin surface. The great majority of these tumors are pigmented nevi and have a benign character which they keep throughout life. However, a significant group among them are the *malignant melanomas* which may develop from a benign nevus or less often may arise on normal skin.



Malignant melanomas are most often observed in patients 40 to 70 years of age and are equally frequent in both sexes. They have rarely been found in the American Negro (Anderson) but have been reported as common among the Negroes of the Anglo-Egyptian Sudan. Hower reported a group of forty-seven cases of malignant melanoma in Negroes of the Sudan, in 75 per cent of which the tumor had developed on the leg and on the plantar region of the foot.

The proportion of malignant melanomas to other forms of cancer of the skin will vary according to the institutions from which they are reported. In our hospital where a great number of rural patients are treated for carcinoma of the skin, there is a malignant melanoma for every thirty-five cases of cancer of the skin.

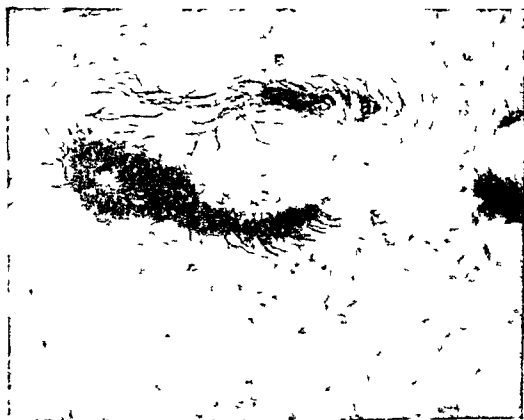


Fig 95.—Benign darkly pigmented hairy nevus of the outer canthus of the eye in a young girl

About 65 per cent of the malignant melanomas develop on a benign nevus (Webster) (Fig 104). Many years may elapse before, explosively or insidiously, the benign nevus becomes malignant. Chronic irritation or trauma may play a role in this transformation. The hairy, fairly large congenital nevus usually light brown in color, is one variant of the benign nevus which practically never becomes malignant. It is also significant that very rarely does a nevus become malignant before puberty. The bathing trunk nevus (Conway) and the naevus unius lateris (Pack) take their name from their unusual appearance and also rarely become malignant.

A rare form of benign nevus, the so-called blue nevus, was found on the skin of the upper extremities and head in twenty-eight of thirty-three patients reported by Webster. It very seldom shows malignant degeneration and is rarely larger than 15 mm, but because of its origin from mesoderm its malignant variant is called melanosarcoma.

### Pathology

**Gross Pathology**—The benign nevus may have many diverse forms, ranging from flat to sessile to papillary (Figs 95 and 96). Sometimes it is hairy,

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## MALIGNANT MELANOMAS OF THE SKIN

### Incidence and Etiology

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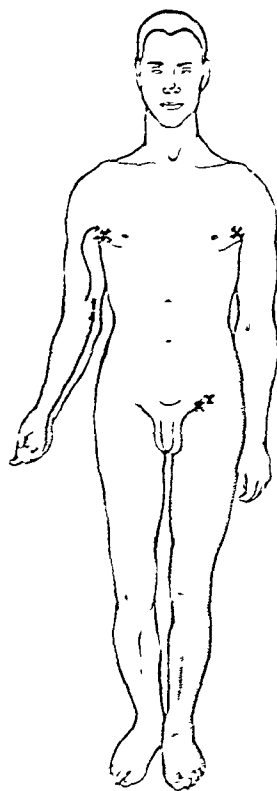


Fig 98—Areas of lymphatic drainage from malignant melanoma of the skin of the head, neck, and lower extremities

and it may vary in color from the normal shade of skin to coal black. The congenital forms, which have less tendency to be pigmented, may spread over a large area.

The malignant melanoma has indefinite margins and is usually deeply pigmented, superficially ulcerated, and very firm. It is very unusual to find it totally nonpigmented. There may be fingers of brownish black pigment extending from the tumor, and, as it grows, well delineated, slightly elevated satellite nodules may be observed. The cut section of the tumor shows the extension to be much deeper and broader than its surface area might indicate.

The pigment in the freckle type of melanoma (Fig 107) is usually not dark. The tumor tends to be rather superficial, spreading peripherally through the outer layers of the skin. The subungual melanoma presents early pigmentation beneath the nail bed and, in the advanced stage, a black fungating ulcer with complete destruction of the bed. These lesions are usually well demarcated, limited by the fascial planes of the distal phalanx. This limitation in spread is similar to that in infection, and therefore this variation of malignant melanoma was designated by Hutchinson as "melanotic whitlow."



Fig 96

Fig 96—Benign papillary pigmented sharply demarcated nevus of the toe



Fig 97

Fig 97—Malignant melanoma arising from the skin of a toe with ulceration and typical sooty halo about the periphery

**METASTATIC SPREAD**—There is no tumor which disseminates more widely or involves more organs than the malignant melanoma. It can, in fact, involve any organ. This is one tumor which, after it has grown through the capsule, may reach veins and disseminate through the blood. Regional lymph nodes, liver and lungs are invariably affected. A malignant melanoma tends to enlarge the organs it involves (the liver very frequently weighs over 5,000 grams), often its metastases are pigmented. This is why it is sometimes designated as the "black death." These metastases, however, may vary in color from nonpigmented to sooty black. The tumor frequently spreads to organs not usually the site of metastases such as the spleen and heart. In 50 per cent of our autopsied cases, the heart showed involvement by tumor.

**Microscopic Pathology**—The microscopic appearance of the nevus may have several variants. The neval cells, however, tend to form small clumps (Fig 101), which, at times, show conspicuous melanin pigment within or just outside their cells. Invariably with careful search some pigment will be found in every nevus. Structures may be found which suggest tactile end organs. At times, it may be very difficult to say whether a nevus is malignant or benign, since it has no boundaries. The blue nevus is made up of interlacing strands of fibrous tissue associated with ribbonlike, melanin-containing cells. Invariably an area of nonpigmented corium is present between the tumor and the epidermis (Montgomery)

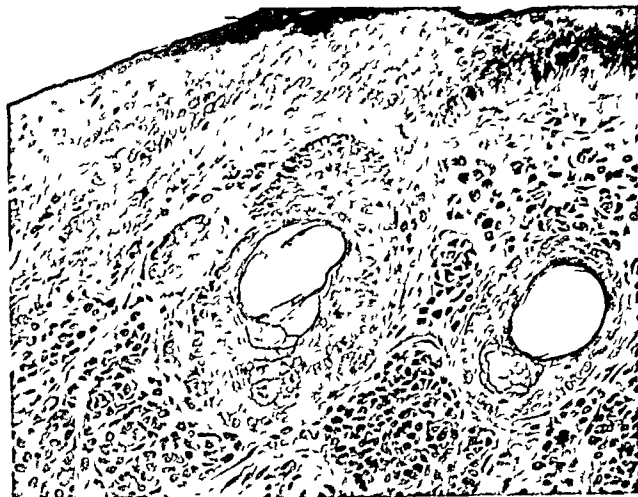


Fig. 101—Photomicrograph of a benign nevus. Note typical arrangement of neval cells in small clusters (low-power enlargement)

The microscopic appearance of the melanocarcinoma is exceedingly variable. It may suggest a basal-cell carcinoma, a fibrosarcoma, or a tumor of nerve origin (Figs 102 and 103). If it is nonpigmented, it may be particularly difficult to diagnose. The amount of melanin varies but, when present, is both within and outside of the cells. In contrast to hemosiderin, which is golden yellow and forms large granules, melanin is rather finely granular and has a brown color. It is not unusual to find very large cells which bear a superficial resemblance to ganglion cells.

If there is considerable pleomorphism with many mitotic figures with invasion of the lymphatics or regional blood vessels, the diagnosis is, of course, not difficult. The greatest difficulty in the microscopic diagnosis lies in certain borderline lesions in which it is hard to determine whether the tumor is malignant or benign. At times, the pigment, in reality melanin, may be considered as hemosiderin and an erroneous diagnosis made, but this can be obviated by doing special stains for iron. The pigmented basal-cell carcinoma, containing melanin pigment, can be mistaken for a malignant melanoma, but the cytologic

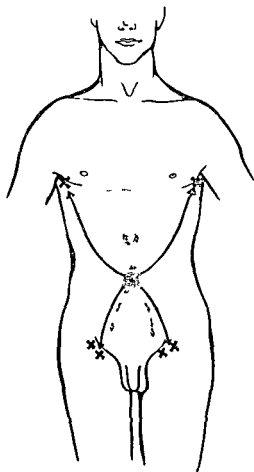


Fig 99

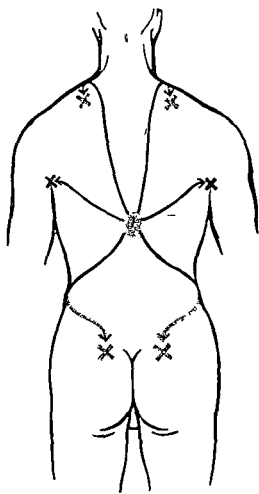


Fig 100

Fig 99—Possible lymphatic pathways of spread of a malignant melanoma located on the skin of the midabdomen

Fig 100—Possible lymphatic pathways of dissemination of a malignant melanoma located in the midlower dorsal region. Dotted lines end in the inguinal lymph nodes

characteristics of the basal cell are usually typical. It should be emphasized that sections taken of suspected melanomas should include areas of transition between normal epithelium and tumor.

### Clinical Evolution

About 65 per cent of all malignant melanomas develop from previously benign nevi. Chronic irritation (for instance, by a belt or by a collar band) can sometimes be directly responsible for the malignant transformation of a

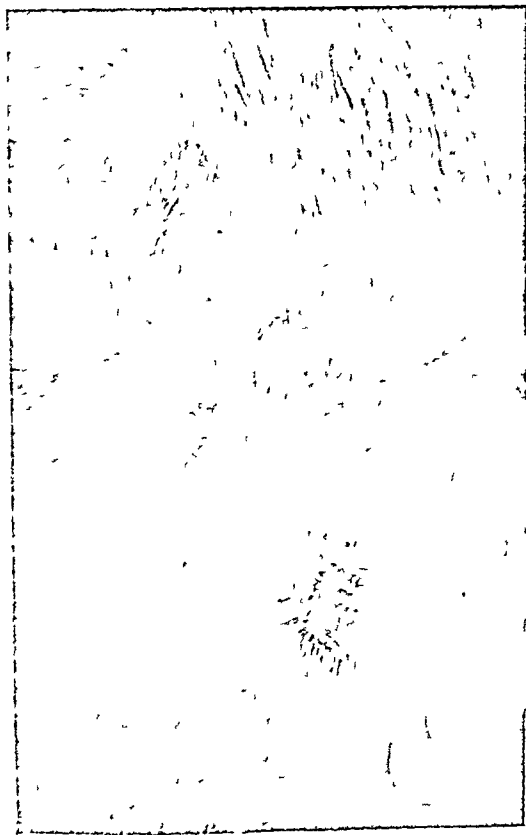


FIG. 104—Malignant melanoma of the preauricular region arising from one of multiple benign nevi of the skin of the face.

benign nevus. There may also be a history of a single trauma or cauterization preceding the change in the character of the tumor. The most significant symptoms of malignant degeneration are *sudden increase in the rate of growth, darkening of pigmentation, ulceration, and bleeding*.

Malignant melanomas are often found in the lower extremities, particularly on the plantar region of the foot, and on the genitals where benign nevi

Fig 102

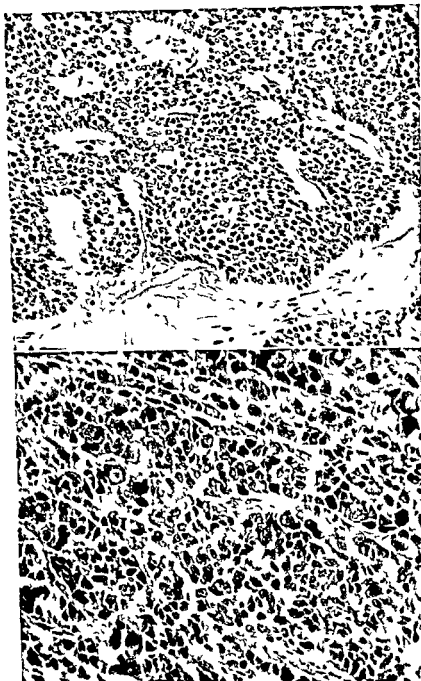


Fig 103

Figs 10 and 103—Photomicrographs of two different malignant melanomas with moderate but equal enlargement. Note dissimilar size of cells and histologic pattern: one superficially resembling a basal cell carcinoma and the other a tumor of nerve origin.



### Treatment

It would be unwarranted and impractical to remove all benign pigmented nevi of the skin on the basis of their chance of developing into a malignant melanoma. However, the excision of all nevi which have been exposed to chronic irritation or have been the subject of trauma is a safe prophylactic procedure.



Fig. 194. Innumerable skin recurrents and cervical lymph node metastases following radical excision and neck dissection for a malignant melanoma of the skin of the face. Tumors can be seen growing through the grafted skin.

A biopsy is indicated whenever a lesion shows signs of malignant degeneration. However, because the early metastasizing character of malignant melanoma has led to the belief that biopsies may cause their rapid dissemination, it is more satisfactory to make a wide excision of all benign or malignant lesions which offer reasonable doubt of their malignant character. This practice applies except when the questionable lesion is located in an area where radical excision would produce deformity. In such a zone there should be no hesitation to biopsy.

are infrequent (Adair) These latter are more frequently seen on the trunk and upper extremities A persistent tumor on the plantar region of the foot, pigmented or nonpigmented, should be considered a malignant melanoma until proved otherwise (Fig 105) This tumor often presents a history of previous inadequate treatment and is commonly diagnosed as a plantar wart or some inflammatory process before the true diagnosis is established



Fig 105—Malignant melanoma arising from the plantar surface of the foot This is a typical point of origin of the tumors Notice diffuse pigmentation This tumor was previously treated as a plantar abscess

### Diagnosis

In the presence of a suspected malignant melanoma, the surrounding skin should be examined meticulously for satellite skin nodules The area of skin pigmentation may extend beyond the apparent limits of the tumor and regional lymph node metastases may appear early The examination should include palpation of the liver, which is the site of frequent voluminous metastases, and a roentgenogram of the chest This thorough investigation will obviate unnecessary surgical treatment

**Differential Diagnosis**—Malignant melanomas may be confused with other lesions of the skin such as the seborrheic wart, the pigmented basal cell carcinoma, the pigmented papilloma some hemangiomas of the skin, and some cases of Bowen's disease which are accompanied by pigmentation

Malignant melanomas are not infrequently associated with neurofibromas of the skin, which may be accompanied by café au lait spots This association is sometimes confusing and has led to errors in diagnosis

Radiotherapy is not recommended for malignant melanomas the majority of which are radioresistant (98 per cent). This lack of radiosensitivity may be explained on the basis of their origin from the neuroectoderm. Radiotherapy has been credited with some local sterilization of melanocarcinomas but in most of these cases the radiotherapy has been used as a necrotizing agent and has brought about an extensive destruction of a limited tumor area and surrounding normal tissue.

*Therapeutic Lymphatic Dissection*—An excision of the involved nodes when they are located in an area of immediate lymphatic drainage is definitely indicated provided of course that there are no distant metastases. This dissection is most successful in tumors of the skin of the head which metastasize to the cervical lymph nodes. The therapeutic dissection of the inguinal nodes is seldom successful because deep inguinal and often iliac node metastases are almost invariably present. In general however a therapeutic lymphatic dissection should be done in spite of the fact that the prognosis for a five-year survival is less than 5 per cent.

*Prophylactic Lymphatic Dissection*—When the tumor is located in an area from which the lymphatic drainage is predictable a radical dissection of the anticipated metastatic node areas is mandatory in spite of the fact that the nodes may not appear clinically involved. The only exception to this rule may be in those patients who develop tumor in the midline of the face or chest for which a bilateral neck dissection or a bilateral axillary dissection would have to be carried out. This is undoubtedly unjustifiable. It would be better, therefore in these cases to wait for the appearance of the metastases.

### Prognosis

Patients with melanomas may be divided into four groups in regard to prognosis. The first with distant metastases when first seen are hopeless and no treatment is indicated. The expected duration of life is from one and one-half to three years. The second with clinically obvious positive regional lymph nodes have a prognosis for a five-year survival of less than 5 per cent even with lymphatic dissection. The third group have clinically negative nodes which are proved positive under the microscope. The prognosis is only fair (probably less than 10 per cent five-year survival). The fourth with the lymph nodes clinically and pathologically negative have a chance for a five year survival of about 30 per cent with prophylactic regional node dissection. The reason for this low percentage of results is the frequent occurrence of hematogenous metastasis.

The site of the lesion will have a direct bearing on the prognosis. If the lesion is located in for example the midabdomen or midposterior chest wall from which lymph drainage is unpredictable or multiple the prognosis is grave (Figs 99 and 100). Because the lymphatics of the lower extremity tend to gravitate to deep nodes beyond the operative field the outlook of lesions there is worse than that of lesions of the upper extremity. Lesions around the head on the whole have the most auspicious future.

The malignant melanomas which very rarely occur in children are extraordinary in that with proper treatment they have an excellent prognosis.

Wide electrocoagulation of the affected area from the periphery to the center has been practiced with the idea that this form of treatment will seal the lymphatics and avoid metastases. This, however, results in unsightly scars and spoils the chance for complete pathologic study of the surgical specimen. Wide surgical excision followed by a skin graft is the accepted form of therapy for all malignant melanomas, and, furthermore, a radical rather than a conservative operation should always be done. This wide cold steel excision permits thorough microscopic examination of the specimen, which is justifiably important. Although an adequate excision is usually made around the tumor not too infrequently is the depth of the tumor underestimated. An inadequate excision may be revealed only by careful pathologic study. Numerous sections should be taken in order to prove the presence of normal margins beyond the tumor area. The deficient removal of a malignant melanoma is inevitably followed by local recurrence, distant metastases, and death. Local recurrences may occur even after wide excisions (Fig 106).



Fig 107—Relatively rare freckle type of malignant melanoma with superficial character

If a tumor is present on the plantar region of the foot and if radical excision is going to result in the impairment of pedal function it is far safer to abandon local excision for a midleg amputation. Similarly, an amputation of the finger is the preferable therapy for a melanocarcinoma of the subungual region.

Because of the occasional dissemination of this tumor through the lymphatics of the skin it has been recommended that these tumors be excised en bloc with the overlying skin and the regional lymphatic nodes. In a lower extremity this would imply quite an extensive removal of skin from the foot to the inguinal region. This procedure is unjustified in our opinion because most malignant melanomas metastasize by embolism through deep lymphatics rather than by permeation of superficial lymphatics.

## Chapter VII

# CANCER OF THE RESPIRATORY SYSTEM AND UPPER DIGESTIVE TRACT

## TUMORS OF THE NASAL FOSSAE

### Anatomy

The nasal fossae are two roughly pyramidal spaces on each side of the nasal septum opening anteriorly through the anterior nares communicating posteriorly with the nasopharynx through the choanae laterally with the maxillary sinus (Fig 108) and superiorly with the sphenoidal sinus the ethmoid cells, and the frontal sinus

The floor of the nasal fossa is formed anteriorly by the superior maxillary bone and posteriorly by the palatine bone covered by the nasal mucous membrane. The roof takes the form of a narrow gutter and is formed by the nasal the frontal the ethmoid and the sphenoidal bones. The medial wall of the nasal fossa is formed by a vertical projection of the ethmoid the vomer and by the cartilages of the nasal septum. The lateral wall runs with a lateral and downward inclination. It is formed by six different bones. From it arise three thin, bony structures the upper middle and lower turbinates presenting a convex surface toward the midline a fixed border on the lateral wall and a free border in the lumen of the nasal fossae each containing part of the space of the nasal fossae the upper middle and lower meatuses.

The orifice opening into the sphenoidal sinus is present in the roof of the nasal fossae. Communication with the ethmoidal cells is found in the superior meatus, the orifices of communication with the maxillary sinus and with the frontal sinus are found in the middle meatus (Fig 109).

Physiologically and clinically the nasal fossa is divided into a lower or respiratory section comprising the inferior meatus the middle meatus the inferior turbinate and the free border of the middle turbinate and an upper or olfactory section above these structures. The *respiratory* portion of the nasal fossa (which is richly vascularized and through which air circulates) is covered by a cylindrical-cell ciliated epithelium, the so-called respiratory epithelium. The cells have a distinct basement membrane goblet cells secreting mucus are interspersed and lymphoid tissue is found but its density is not very marked except near the posterior choanae. Sparse pigmented cells are found in the submucosa. Metaplasia of the cylindrical epithelium toward squamous epithelium is very commonly found. The upper or *olfactory* section of the nasal fossa lies above a hypothetical horizontal line passing at the level of the free border of the middle turbinate. This is a narrow space through which air does not circulate. It is not as well vascularized and is rich in yellow pigment the locus luteus. The olfactory nerve distributes its fine fibrils over this area.

even if regional node metastases are present. These metastases, as a rule, are infrequent. The so called malignant freckle type and the subungual type seem to have a more fortunate outlook than has the usual melanocarcinoma.

Previous inadequate treatment causes delay and gives time for metastases to occur. Patients with such a history have a very ominous prognosis. Of thirty patients admitted to our hospital who were previously treated by zinc chloride paste, radiotherapy, or inadequate surgery, only three are living without disease five or more years later.

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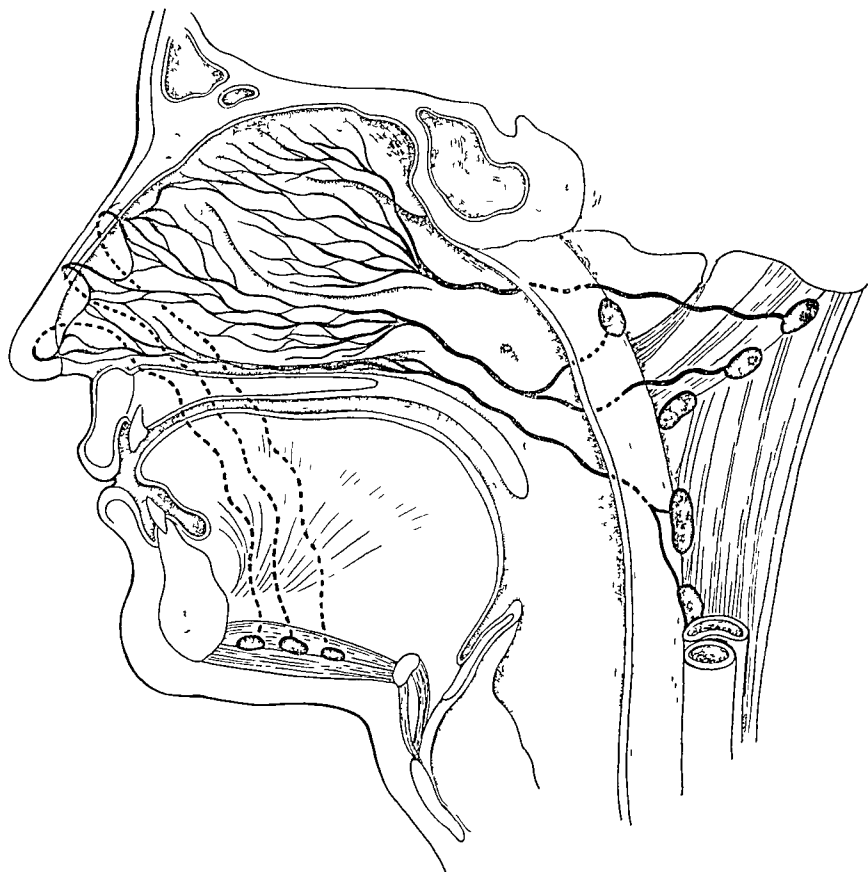


Fig 110 — Anatomic sketch of the lymphatics of the nasal fossa. The anterior lymphatics lead to the submaxillary lymph nodes; the posterior lymphatics are drained by the retropharyngeal and anterior jugular nodes.

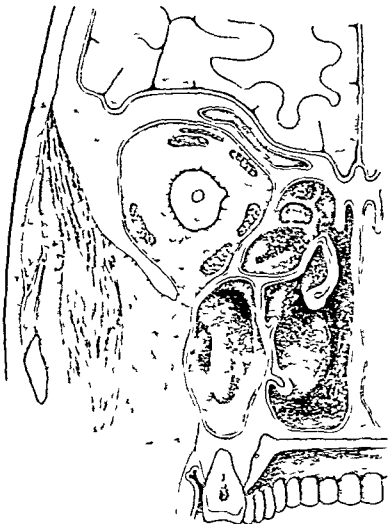


Fig 108 —Anatomic sketch of a frontal section of the skull demonstrating the upper and lower portions of the nasal fossa and its close relationship to the maxillary sinus, the orbit, frontal sinus and the brain (After Te tut)

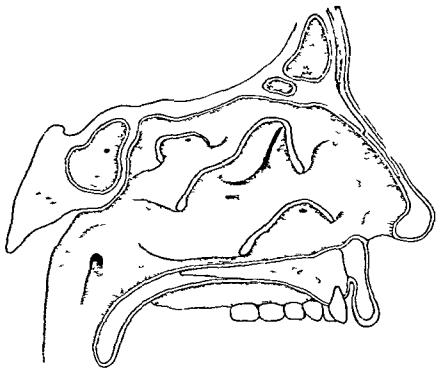


Fig 109 —Lateral view of the nasal fossa. Parts of the turbinates have been removed in order to demonstrate openings which establish communication with the maxillary sinus and frontal sinus.



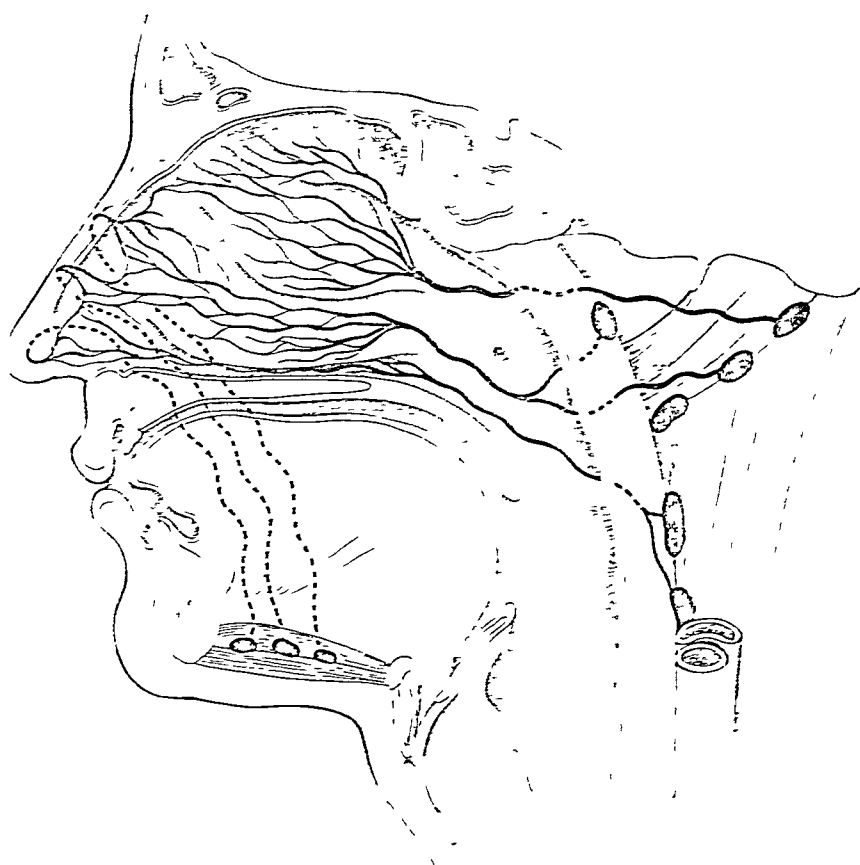


FIG. 140.—Sagittal view of the lymphatic system of the head and neck. The anterior lymphatic chain is the superficial lymphatic system; the posterior lymphatic chain is the deep lymphatic system.

**Lymphatics**—The *anterior* lymphatics follow a forward direction, pass between the cartilages to reach the teguments of the face, and become continuous with the superficial lymphatics of the skin of the nose and cheek. The *posterior* lymphatics gather into three main trunks—an upper group, which drains the superior turbinates and leads to the retropharyngeal lymph nodes, a middle group, which drains the lower turbinate and lower meatus and passes under the eustachian tube to end in the deep nodes of the internal jugular chain, and a lower group that includes most of the lymphatic drainage of the floor of the nasal fossae and septum which follows the direction of the soft palate and joins the lymphatics of the tonsil to terminate in the lymphatics of the anterior jugular chain (Fig. 110)

### Incidence and Etiology

Benign and malignant tumors of the nasal fossae are rare and even in approximate incidence cannot be computed as the cases have been so very sporadically reported. MacComb found that only sixty-five patients with malignant tumors of the nasal cavity had been seen at the Memorial Hospital of New York in a period of thirteen years.

Malignant tumors of the nasal fossa are found in men as well as in women but the proportion of women with malignant tumors of the nasal fossae seems to be slightly larger than that which in general is found for cancer of the upper air passages.

### Pathology

**Gross and Microscopic Pathology**—Although tumors of the nasal fossae are relatively rare this region is the site of origin for a variety of benign and malignant tumors the histogenesis of which may be quite difficult to establish.

The most common growths of the nasal fossae are *polyps*. These are usually associated with inflammatory lesions but may also accompany malignant tumors of the nasal fossae and accessory sinuses. Nasal polyps are usually fibroepithelial tumors arising from the lower turbinate. They are characteristically pedunculated and may rarely become ulcerated. The bulk of the tumor is formed by loose edematous connective tissue but sometimes it may present cystic dilatations which may lead to the diagnosis of cystadenoma (Geschel'ter). True *papillomas* of the nasal cavity are very rare. They are usually inflammatory and are found most frequently in men in the fourth decade of life. They are hard and on microscopic examination show fibrous stroma and thick epithelium. Hall divides them into cylindrical squamous and mixed types. *Adenomas* of the nasal mucous membrane are also rare. They are polypoid growths arising in the ethmoidal region the turbinates or the septum. They may be pedunculated or sessile and may grow to be several centimeters in diameter. They are seldom ulcerated. Microscopically adenomas appear as glandular hyperplasia with rich mucous secretion. The stroma may be dense and fibrous and calcified deposits may be present. They have been considered as potentially malignant tumors but this is not generally recognized (Rosenberg). Papillary and cavernous *hemangiomas* may also arise

particularly from the septum and lower turbinate. They have the shiny bluish appearance of hemangioma developing under mucous membrane.

*Plasmacytomas* are rare tumors of the upper air passage which most often appear in the nasal fossa. They are similar to tumors arising from the bone marrow usually described as multiple myeloma. But the extramedullary plasma-cell tumor is not frequently observed. Hall is found only 127



Fig. 110—Photomicrograph of the tumor in the nasal fossa and upper part of the maxilla.

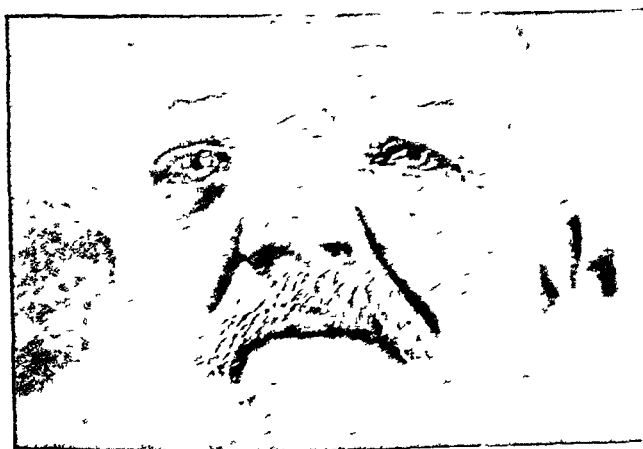


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An important group of tumors arising from the nasal fossa and also from the accessory sinuses are the *mucous and salivary gland tumors*. They arise from the floor of the nasal fossa and from the ethmoid region. The true incidence of this type of tumor has been underestimated. In general these tumors are benign the malignant variant cannot always be diagnosed with biopsy. The majority are well encapsulated and destroy surrounding tissue by unrelenting expansion. Their histologic character is varied and for this reason they have been reported under a large number of labels, adenocarcinomas, chondrosarcomas, endotheliomas, myxochondromas, etc. (see Tumors of the Salivary Glands page 618). They include such tumors as cylindromas, basalomas and the so-called mixed tumors. Some of them may be confused with cylindrical-cell carcinomas but in the mucous and salivary gland tumor the cell polarity is inverted and irregular and the secretory products are excreted not only in the lumen but also between the cells and in the stroma (Ringertz). They are of epithelial origin (Krompecher) and present a great polymorphism, although identical in nature with tumors of the major salivary glands, they also develop in the oral cavity (see Tumors of the Hard Palate page 206), larynx, and trachea and from lacrimal and salivary glands. Increased knowledge of these tumors has resulted in their grouping under the heading of mucous and salivary gland tumors (Albion).

The most common malignant tumors of the nasal fossae are the *epidermoid carcinomas*. They usually arise from the middle and inferior turbinates and also from the ethmoidal region and septum. The majority of these tumors are polypoid or papillary becoming at times superficially necrotic. They invade the thin wall which separates the nasal fossa from the maxillary sinus and penetrate the antrum. They may produce obstruction of the lacrimal duct and also may be accompanied by frontal sinusitis. *Adenocarcinomas* most often arise from the region of the olfactory mucous membrane or from the glands. They are the malignant counterpart of the adenomas. These tumors diffusely invade the thin bone of the area and extend to one or both orbits with consequent displacement of the eye. They also extend to the nasopharynx and to the base of the skull resulting in early invasion of the cranium. Histologically adenocarcinomas may present a pseudopapillary arrangement covered by a single layer of epithelium greatly resembling that of an adenocarcinoma of the large bowel (Ringertz). These tumors however may present themselves as adenoma-like mucus-forming malignant tumors which have also been called *cylindrical-cell carcinomas*. Hautant considered them as typical tumors of the ethmoid region. They are formed by cylindrical or prismatic cells similar to those seen on the olfactory mucosa. Mucus is secreted more or less abundantly giving the tumors a peculiar soft consistency which is responsible for their being called colloid carcinomas. Sometimes the mucus is not abundant and bone formation is found within the tumor. This may be fragments of the invaded bone or may be a distinctive feature of the tumor. They rarely invade the frontal and sphenoidal sinuses but these are usually filled with polypoid masses (Hautant).

cases reported from 1905 to 1942, sixty three originated in the upper air passages and thirty seven of these presented lesions in the nasal fossa. Plasmacytomas may be benign may show evidence of local malignancy with diffuse infiltration but no metastases or they may have all the characteristics of malignant tumors and metastasize to lymph nodes and bones. Most of these tumors are single but many some benign and some malignant, are multiple. Other sites of predilection are the nasopharynx, the antrum the larynx, and the oral cavity. Histologically the abundance of plasma cells is their characteristic feature. Most of the malignant cases present a more atypical cell structure a greater variation in size and form of the cells and nuclei, more mitotic figures, and a much more delicate reticulum than in the benign varieties (Ringertz). But these differences are not pronounced enough to establish definite criteria of malignancy (Hellwig). They are composed of cells which



Fig 113 —Local invasion of the ethmoid region of the nasal fossa by a meningioma. Note chemosis and lateral deviation of the right eye.

resemble normal plasma cells with little connective tissue and are often described as granulomas. Not infrequently numerous cells of various sizes may be observed. The majority of these tumors are inflammatory but some of them are or become malignant. Their benignity or malignancy however is difficult to diagnose on histologic examination. *Myxomas* may arise from the ethmoidal region. They are characteristically soft slowly growing tumors which microscopically show a typical synovium. Whether these tumors may degenerate into *myxosarcomas* is questionable. *Chondromas* and *chondrosarcomas* may arise from the cartilage of the nasal septum and in the ethmoid (Wirth). *Enchondromas* have been reported arising from the ethmoidal region or at the junction of the septum and the floor of the nasal fossa. *Fibro osteomas* may arise from the ethmoid (Billing). *Neurilemmomas* have also been reported to arise in the nasal fossa in the form of a firm, reddish, nonulcerated mass (Bogdasarian). Most of these tumors are pathologic rarities.

Pain is a very important sign, for it is rarely present in benign tumors unless caused by concomitant sinusitis. In malignant tumors the pain is progressive and severe.

Some of the malignant tumors of the nasal fossa develop relatively fast, facilitating the clinical diagnosis, but others, such as the cylindrical-cell carcinomas of the ethmoid and the malignant variety of the mucous and salivary gland tumors, may develop slowly over a period of years without evidence of metastases. Some cases of plasmocytoma present a fast evolution, but others develop slowly and may recur years after treatment (Baldenweek, Piney)



Fig. 114—Carcinoma of the ethmoid having invaded anteriorly through the soft tissues and ulcerated the skin of the naso orbital region.



Fig. 115

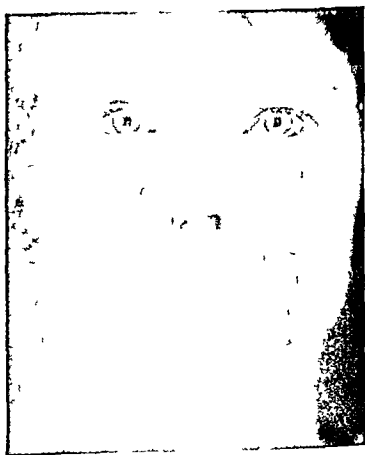


Fig. 116

Fig. 115—Adenocarcinoma of the posterior ethmoid with exophthalmos and lateral deviation of the right eye.

Fig. 116—Same patient following unsuccessful roentgentherapy to the primary lesion. A submaxillary metastasis developed.

Ewing described a special form of tumor supposedly arising from Schneiderian membrane and questionably constituting an entity. Stewart believes that these tumors are actually epidermoid carcinomas.

Tumors presenting nervous system characteristics have been observed in the nasal cavity. It has been suggested that they may arise from the neural fibers of the olfactory nerve (Berger). *Gliomas* supposedly arising from embryonal detachments of the central nervous system or from the olfactory area have also been reported in this area. *Melanomas* not infrequently have been observed in the nasal fossa. They arise from the septum or turbinates and usually have satellite mucosal nodules. They are gray, blue, or black in color.

*Lymphosarcomas* are the second most frequent malignant tumor of the nasal fossa. They develop from lymphoid tissue which is particularly dense around the choanae. More often lymphosarcomas found in this area have originated in the nasopharynx and invaded the nasal fossa secondarily. They are soft and rapid growing and produce a deformity of the nose. They invade the maxillary sinus and the orbit. *Lymphoepitheliomas* of the nasal fossa are rather rare. They also develop near the choanae.

**METASTATIC SPREAD**—Metastases to the retropharyngeal lymph nodes from tumors arising in the olfactory area are rare, but they are more frequent than is suspected from malignant tumors of the respiratory area of the nasal fossae. Metastases to the submaxillary region are occasionally seen (Fig. 116) and distant blood borne metastases to the lungs, liver, brain, and bones have also been observed (MacComb). Ringertz found only two cases of distant metastases in twenty-seven reported cases of cylindrical cell carcinoma. Lymphosarcomas may present cervical or mediastinal metastases early in their development. Hellwig collected nine cases of plasmocytomas which had metastasized to bone and four of them also had lymph node metastases. Seven of the cases presented primary lesions in the nasal fossa.

### Clinical Evolution

Whether a tumor of the nasal fossa is benign or malignant, the most common presenting symptoms are nasal obstruction, nasal discharge, and epistaxis. Tumors which develop in the respiratory section of the nasal fossa may rapidly produce obstruction and later deformity of the nose (Fig. 111), deviation of the nasal septum, and partial obstruction of the opposite fossa. Tumors of the olfactory region, on the other hand, usually give a partial bilateral obstruction which only becomes complete in very advanced cases. When tumors of the ethmoid region develop posteriorly, they may invade the nasopharynx. When they develop anteriorly, they flatten the bridge of the nose, may invade the skin, and ulcerate at the inner canthus of the eye (Fig. 114). Sometimes there is simple lateral displacement of the eye with some exophthalmus and chemosis. As the tumor increases and invades both orbits, the eyes become widely separated (Fig. 112) but as a general rule the movements and the vision of the eye are preserved. Nasal discharge and epistaxis may or may not be present but no conclusions can be drawn from the intensity of the bleeding for benign tumors very frequently bleed more than malignant tumors.



These lesions are very successfully treated by means of radiations (Esquerria-Gómez, Brigard) Tumors of the ethmoid may be confused with the very rare primary tumors of the frontal sinus. The tumors of the frontal sinus, however, are strictly unilateral and displace the eye laterally and downward (Fig 121)

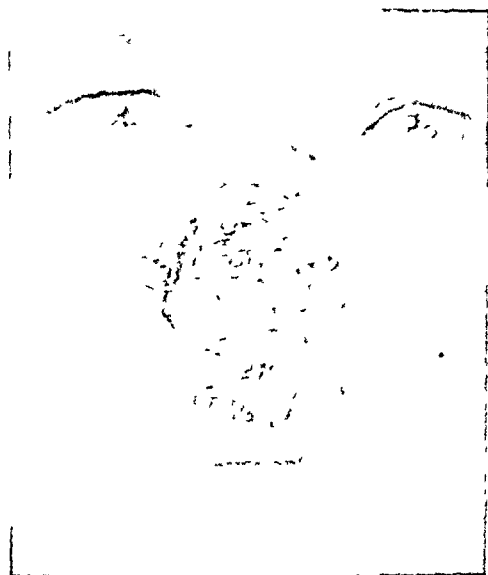


Fig. 120 — Typical syphilitic lesion of the nose showing an erythematous and scrofulous appearance

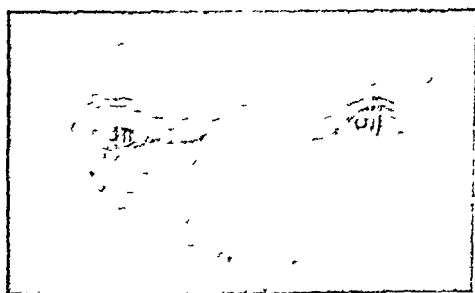


Fig. 121 — Carcinoma of the right frontal sinus with lateral and downward deviation of the eye

A roentgenologic examination is helpful in establishing the diagnosis. Some forms of tertiary syphilis of the nasal fossa may be histologically confused with lymphosarcoma (Proby). Others which are ulcerated may be taken for carcinomas. On histologic examination the syphilitic lesions present a protean appearance, but their nature is usually suspected by their granulomatous character and a positive serologic test (Fig 120). Rarely meningiomas of uncer-

A variety of secondary symptoms may appear such as lachrimation and dacryocystitis due to compression of the lacrimal duct. These signs are particularly common in ethmoid tumors (Ohngren). Symptoms of frontal and maxillary sinusitis may also be present.

Early metastases do not occur in most malignant tumors of the nasal fossa with the exception of the lymphosarcoma, which may metastasize to the submaxillary region and mediastinum to cause symptoms before the primary lesion is suspected. In these cases the discovery of the primary lesion in the nasal fossa is only a consequence of the perspicacity of the examiner. Epidermoid carcinomas may metastasize to the retropharyngeal and submaxillary regions. Other malignant tumors of the nasal fossa metastasize predominantly to distant organs through the blood stream. Plasmocytomas metastasize to bones and in some cases the development of an osseous metastatic marks the clinical onset (Ringertz). Death usually results from lack of control of the disease, continuous bleeding, deterioration of the general condition, hemorrhage or meningeal or respiratory complications.

### Diagnosis

The diagnosis of tumors of the nasal fossa requires a careful evaluation of the history, a thorough anterior and posterior rhinoscopy, multiple roentgenographic studies, and a skilled appraisal of the histologic character of the tumor.

The anterior rhinoscopy often only reveals evidence of turbinate edema, and profuse bleeding may interfere with proper visualization. Only repeated examinations can overcome these difficulties. Posterior rhinoscopy is particularly helpful in tumors of the ethmoid. This examination may be best done with a rubber catheter as a soft palate retractor (see Diagnosis of Tumors of the Nasopharynx, page 138). Profuse bleeding after removal of benign polyps in an aged patient should be carefully investigated (Moutant). Benign polyps are often due to and found together with malignant tumors of the nasal fossa and maxillary sinus. The removal of a polyp under these circumstances may provide some improvement but may delay the proper diagnosis.

Little of value can be said about the aspect of these lesions for their clinical differentiation. Papillary bleeding tumors may be either benign or malignant, and a smooth nonulcerated mass may sometimes hide a malignant tumor. Melanomas are easily recognized because of their grayish black color, but special stains are necessary to ascertain the presence or absence of melanin pigment. Hemangiomas have a typical shiny bluish appearance but this may be obscured by excessive bleeding. Benign plasmocytomas are often pedunculated while the malignant variety is usually ulcerated, both are rare before the age of 40 years.

**Roentgenologic Examination.**—The radiographic examination of the skull may be extremely valuable. In benign tumors which produce obstruction, there may be edema and opacity of the nasal for a and accessory sinuses. When displacement occurs there is not an actual bone destruction. In malignant tumors the same elements are present. In addition there is an oblique

exception of epidermoid carcinomas and lymphosarcomas, a wide surgical excision is the preferred treatment for most of the malignant tumors of the nasal fossae and is also the only hope of cure. Denker proposed a resection of the superior maxilla, including the ethmoid. Holmgren performs a similar operation but prefers the use of electrosurgery, also advocated by New and many others. Hantant and Monod perfected a technique for the removal of ethmoidal tumors consisting of a block resection of the ethmoid including part of the floor of the orbit and the upper and middle turbinates (Fig 122). The operation is always followed by intracavitary curietherapy and, in their hands, gave interesting results. It was attended, however, by serious complications such as meningitis, hemorrhages, radionecrosis, loss of the eye, etc.

**RADIOTHERAPY**—Although an intracavitary application of radium may be given after a wide surgical excision of the tumor, the burden of the treatment rests on the surgical intervention. Lymphosarcomas and epidermoid carcinomas of the nasal fossae should be treated by roentgentherapy alone. The external radiotherapy must be administered so that the tumor is homogeneously irradiated with a sufficient dose for its sterilization. The commonest error with lymphosarcomas is the administration of an inadequate dosage. Adenocarcinomas of the ethmoid are seldom sterilized by external irradiation and should preferably be treated by surgery when possible. The effectiveness of roentgentherapy in plasmocytomas has not been thoroughly tried.

### Prognosis

Benign tumors of the nasal fossae have a tendency to hemorrhage or to become infected, and for this reason the prognosis is not always good. When they are advanced and require extensive surgical procedures, the operative risk is naturally high.

Hantant treated twenty one patients with ethmoidal tumors, with nine living from four to twelve years after operation. These ethmoidal tumors included salivary gland tumors, cylindrical-cell carcinomas, and adenocarcinomas. Ohngren reported on fifty-seven patients treated with electrosurgery, with 42 per cent living three years. Ringertz collected six cases of melanoma in which the patients were surgically treated, two patients lived for three years but there were no permanent cures. Piney and Riach reported a case of plasmocytoma which recurred twelve years after treatment.

The prognosis of adenocarcinomas is very poor. MacComb reported a five year survival in only one of seven patients with adenocarcinomas. Ringertz reported that eight of eighteen patients with cylindrical-cell carcinoma remained well five years after treatment. MacComb reported five-year survivals in four (23 per cent) of seventeen patients with epidermoid carcinoma of the nasal fossa treated by various methods at the Memorial Hospital in New York.

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tain origin (optic nerve, cerebral or meningeal tissues, or a congenital fault in the region of Schneiderian membrane) can develop in the orbit and be confused with malignant neoplasms of the ethmoid (Fig 113)

### Treatment

**SURGERY**—The treatment of the different tumors of the nasal fossae varies considerably, depending on the nature of the lesion at hand. An accurate diagnosis is consequently necessary before therapy is chosen. Most of the benign tumors can be adequately excised through the anterior naris. By this



Fig 122—Radical resection of ethmoid tumors. The operation is successful particularly in the treatment of localized and well-differentiated malignant tumors and in the treatment of mucinous and salivary gland type of neoplasms of the ethmoid. (From Hiantant A, courtesy of Radiophys et radiothérapie 193)

process the tumor very often has to be morseled and some of the lesions may eventually recur because obviously the excisions may be incomplete. Some benign tumors, however, may be encapsulated and so large that a major surgical procedure is required to remove them in toto. A lateral rhinotomy followed by curettage (Harmer and Glas) is sometimes necessary for advanced benign tumors. In plasmocytomas a wide resection is preferable. With the

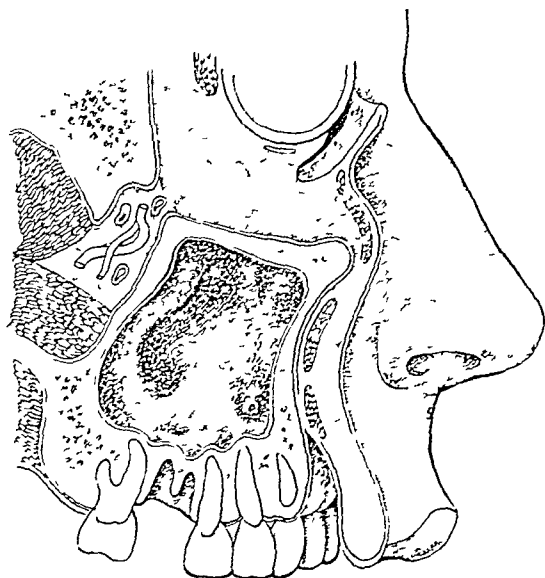


Fig 123—Sagittal section of the right maxillary sinus showing its close relationship with the dental roots the floor of the orbit and the pterygomaxillary fossa

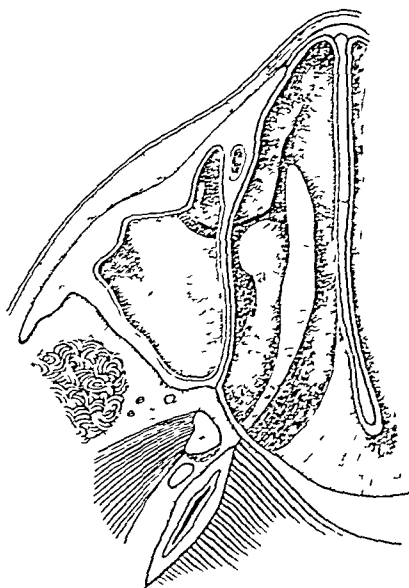


Fig 124—Transversal section of the right maxillary sinus revealing its close relationship with the nasal fossa and pterygomaxillary muscles (After Testut.)

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## CARCINOMA OF THE MAXILLARY SINUS

### Anatomy

The maxillary sinus occupies the center of the superior maxillary bone. Roughly it forms a triangular pyramid with its base toward the nasal fossa and its summit toward the malar region. The anterior wall corresponds to the cheek and the canine fossa and extends up to the border of the floor of the orbit. The roof or upper wall corresponds to the floor of the orbit and the posterior wall is related to the pterygomaxillary fossa (Figs 123 and 124). The base is formed by a thin wall divided in two by the insertion of the inferior

and further extension to the hard palate is sometimes accomplished at the level of the last gross molar.

Less often carcinomas of the antrum originate in the *suprastructure*, usually laterally at the summit of the snusal pyramid. They rapidly invade the malar bone and the outer half of the floor of the orbit, and later extend to the temporal fossa (Fig. 127). The skin is at first only distended but may later be invaded. Less frequently, the tumors of the suprastructure develop medially, rapidly invading the ethmoid and the inner half of the floor of the orbit, extending anteriorly at the level of the naso-orbital region (Fig. 128). Invasion of the orbit is rarely followed by invasion of the eye, usually the eye is only displaced.

Whether carcinomas of the maxillary sinus arise in the *infrastructure* or suprastructure, they may extend throughout the antrum and to surrounding structures in every direction. In advanced cases, invasion of the floor of the orbit and the malar bone is frequent, and there may be some extensive destruction of the alveolar process. Extension to the pterygomaxillary structures is almost constant in terminal cases. Ulceration of the markedly distended soft tissues of the cheek occurs only in the late stage of the disease. With secondary infection an accompanying pansinusitis often results.

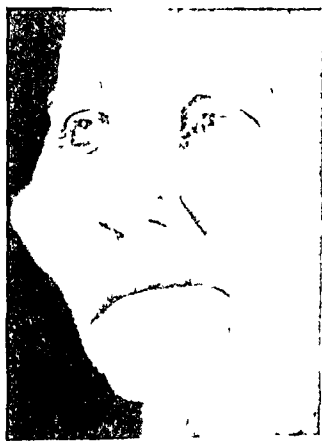


Fig. 126.—Advanced carcinoma of the *infrastructure* of the maxillary sinus with typical deformity of the interorbital wall and filling of the nasal cavity.

**Metastatic Spread**—Metastases from carcinomas of the maxillary antrum are observed only in late stages. They usually appear in the submaxillary and cervical lymph nodes. Rarely there may be metastases to the retropharyngeal lymph nodes. Tumors of the suprastructure which develop laterally may invade the subcutaneous tissues and metastasize to the preauricular lymph nodes. Distant metastases are uncommon.

**Microscopic Pathology**—The overwhelming majority of tumors of the antrum are moderately differentiated epidermoid carcinomas developing by

turbinate The orifice of communication between the maxillary sinus and the nasal fossa is found in the upper half of this wall The maxillary sinus is lined by a columnar ciliated epithelium

**Lymphatics**—The lymphatics of the maxillary sinus communicate with those of the nasal fossa and consequently end in the retropharyngeal, sub maxillary, and anterior jugular lymph nodes

### Incidence and Etiology

Malignant tumors of the maxillary sinus are by far the most common forms of tumor in this region New (1935) reported that they occur three times as often in men as in women Chronic sinusitis does not seem to predispose to carcinoma of the maxillary antrum These epithelial tumors constitute a majority of the malignant neoplasms developing in this area

### Pathology

**Gross Pathology**—The majority of carcinomas of the maxillary sinus originate in the *infrastructure* (or lower half) in close contact with the dental roots and their nerves They expand the anterolateral wall of the sinus, distend the soft tissues (Figs 125 and 126), and very rarely invade and ulcerate them



Fig. 15—Carcinoma of the infrastructure of the maxillary sinus with typical external deformity

In their downward extension, they produce a filling of the upper gingivobuccal gutter and cause enlargement of the upper gingiva, loosening the anterior molars and bicusps, and finally ulcerating the gingiva and extending sub mucosally to involve the entire half of the hard palate They displace the nasal turbinates medially and produce relative nasal obstruction but rarely ulcerate the tissues of the nasal fossa Tumors of the infrastructure very seldom develop posteriorly Such rare posterior tumors of the infrastructure rapidly invade the pterygomaxillary fossa and the posterior ethmoidal cells



metaplasia from the cylindrical mucosa. Keratinization is shown by isolated foci rather than by epithelial pearls (Fig 129). Large clear cells presenting nuclear monstrosities are often observed resembling those seen in recently irradiated carcinomas (Fig 130). Mitoses are usually numerous.

Fig 129



Fig 130

Fig 129—Typical carcinoma of the maxillary sinus showing little differentiation.

Fig 130—Epidermoid carcinoma of the maxillary sinus showing multiple clear cells, abundant mitoses, and frequent nuclear monstrosities.

Adenocarcinomas and cylindrical-cell carcinomas have been reported arising in the maxillary antrum (Thomas), but it may be that many of these are actually malignant forms of mucous and salivary gland tumors which

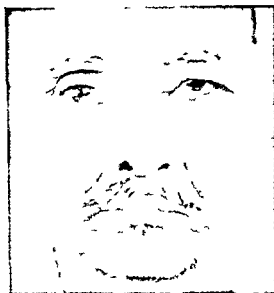


Fig 12—Carcinoma of the suprastructure of the maxillary sinus developing laterally invasion of the floor of the orbit with inward displacement of the eye (Courtesy of Dr Carlos Gárciga Department of Poentgentherapy Instituto del Radium Havana Cuba )

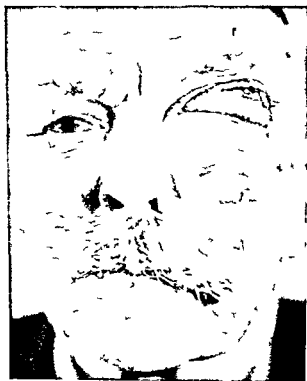


Fig 12B—Carcinoma of the suprastructure of the maxillary sinus developing medially with exophthalmos chemo is and lateral displacement of the eye

metaplasia from the cylindrical mucosa. Keratinization is shown by isolated foci rather than by epithelial pearls (Fig 129). Large clear cells presenting nuclear monstrosities are often observed, resembling those seen in recently irradiated carcinomas (Fig 130). Mitoses are usually numerous.

Fig. 129



Fig 130

Fig 129—Typical carcinoma of the maxillary antrum showing little differentiation

Fig 130—Epidermoid carcinoma of the maxillary sinus showing multiple clear cells, abundant mitoses and frequent nuclear monstrosities

Adenocarcinomas and cylindrical-cell carcinomas have been reported arising in the maxillary antrum (Thomas), but it may be that many of these are actually malignant forms of mucous and salivary gland tumors which

sometimes arise in this area. Rare tumors such as malignant melanomas and neurilemmomas have also been reported arising in the maxillary antrum. Lymphosarcomas found in this area probably originate in the nasopharynx and invade the antrum secondarily. This is observed particularly in children.

### Clinical Evolution

The majority of patients with carcinomas of the maxillary antrum first complain of a toothache, loosening of teeth, inability to apply a dental plate, or a superior maxillary tumefaction suggesting a dental abscess. An antero-lateral tumefaction is typical of most tumors of the infrastructure and may appear without giving any symptoms. This tumefaction distends the soft tissues, which become reddened, and may finally ulcerate. Oral extension of the tumor appears as a smooth, nonulcerated tumefaction of the upper gingiva and hard palate. An ulceration may occur in the upper gingiva, around the teeth, or through a tooth socket. The tumor may extend beneath the mucosa to involve the entire half of the hard palate. The rare tumors of the infrastructure which develop posteriorly show no external tumefaction; they are attended by diffuse pain and trismus.

In carcinomas of the superstructure, nasal discharge and epistaxis may be the first symptom, followed by an external tumefaction in the malar region or the naso-orbital area. Lacerimation and dacryocystitis may also occur. Trismus is seldom an early symptom except in the very few tumors which develop near the posterior wall and invade the pterygomaxillary fossa. In general there is little or no initial pain, but as the tumor develops and particularly as it invades the floor of the orbit, pain in the infra-orbital region may become intense. There may be a burning sensation and other paresthesias along the distribution of the superior maxillary nerve.

In tumors of the superstructure developing medially the ethmoid region and the floor of the orbit are invaded early. There is an external tumefaction in the naso-orbital region and the eye is displaced laterally. The movements of the eye are seldom affected and chemosis is not frequently observed but dacryocystitis frequently completes the picture. In tumors of the superstructure developing laterally an external tumefaction appears first in the malar region later extending to the temporal fossa. The eye is displaced medially and there is frequently marked chemosis but no impairment of the movements of the eye (Fig 142). Invasion of the skin with secondary infection results in late stages.

Carcinomas of the maxillary antrum do not metastasize early. Those which ulcerate into the oral cavity most frequently present a submaxillary and upper cervical metastasis. Tumors of the superstructure which develop in the malar region may have a precuticular adenopathy when the subcutaneous tissues have been invaded (Regato). Distant metastases are very infrequent.

The majority of patients with carcinoma of the maxillary antrum in whom the disease is not controlled by treatment die from local spread, hemorrhage, bronchopneumonia, undernourishment and cachexia.

### Diagnosis

The early diagnosis of carcinomas of the maxillary sinus is unfortunately seldom made. Because of the frequency of dental symptoms, a large responsibility for their early detection lies on the dental profession. Unfortunately, the symptoms are usually interpreted as due to other more common benign conditions, and, in general, teeth extractions and curettements or even small surgical interventions are attempted before the true diagnosis is established.



Fig 131—Roentgenogram of a carcinoma of the maxillary antrum with complete destruction of the floor of the orbit and invasion of the anterior ethmoid cells.

The clinical examination should include palpation of the tumor area, including the floor of the orbit, the hard palate, and the upper gingivobuccal gutter. Anterior rhinoscopy may reveal narrowing of the nasal fossa or the presence of concomitant polyps, rarely is tumor directly accessible through the nasal fossa. Posterior rhinoscopy should be carried out to eliminate the possibility of the tumor having originated in the nasopharynx and invaded the antrum secondarily.

**Roentgenographic Examination**—The roentgenographic examination is of great value in establishing the true extent of the lesion and the amount of bone destruction, particularly of the floor of the orbit, malar bone, and hard palate (Fig 131). The radiographic examination is not diagnostic in early cases (Fig 132), for the only abnormality is a clouding of the sinus (Pfahler)

sometimes arise in this area. Rare tumors such as malignant melanomas and neurilemmomas have also been reported arising in the maxillary antrum. Lymphosarcomas found in this area probably originate in the nasopharynx and invade the antrum secondarily. This is observed particularly in children.

### Clinical Evolution

The majority of patients with carcinomas of the maxillary antrum first complain of a toothache, loosening of teeth, inability to apply a dental plate or a superior maxillary tumefaction suggesting a dental abscess. An antero-lateral tumefaction is typical of most tumors of the infrastructure and may appear without giving any symptoms. This tumefaction distends the soft tissues, which become reddened, and may finally ulcerate. Oral extension of the tumor appears as a smooth, nonulcerated tumefaction of the upper gingiva and hard palate. An ulceration may occur in the upper gingiva, around the teeth, or through a tooth socket. The tumor may extend beneath the mucosa to involve the entire half of the hard palate. The rare tumors of the infrastructure which develop posteriorly show no external tumefaction, they are attended by diffuse pain and trismus.

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Carcinomas of the maxillary antrum do not metastasize early. Those which ulcerate into the oral cavity most frequently present a submaxillary and upper cervical metastasis. Tumors of the suprastructure which develop in the malar region may have a preauricular adenopathy when the subcutaneous tissues have been invaded (Reggio). Distant metastases are very infrequent.

The majority of patients with carcinoma of the maxillary antrum in whom the disease is not controlled by treatment die from local spread, hemorrhage, bronchopneumonia, undernourishment and cachexia.

and malignant tumors of the superior maxillary region may offer difficulties in clinical differential diagnosis, but most of them are easily differentiated when a biopsy is available

*Dentigerous cysts* usually occur in young adults, cause no symptoms, but may grow to considerable size. When they contain a tooth, their diagnosis is easily made by roentgenographic examination. *Odontomas* are tumors in which two or more tissues of the tooth germ are present (enamel, dentine, cementum). They occur in young individuals, are directly caused by faulty tooth formation, and may be solid or cystic. Radiographic examination reveals the presence of one or more teeth, and the enamel may have a radial arrangement.

*Ameloblastomas* occur in the superior maxilla much less frequently than they do in the mandible. In a review of 379 cases, Robinson found only 16 per cent in the upper jaw. There was an almost equal distribution in both sexes and the average duration of the tumor was eight and one-half years. Although they have been found in a 4-month-old baby as well as in older individuals, they are most frequently found in patients 25 to 35 years old. There may be a history of unerupted tooth or trauma. The tumors develop very slowly without pain, and become ulcerated and secondarily infected in the oral cavity only after teeth have been extracted. They are surrounded by a thick shell of bone. Some of them are cystic and others are solid. In the cystic variety, the cavities are lined with a smooth membrane and the cysts contain a clear yellowish fibrinous fluid and are separated by thin bony walls. Their histologic appearance is characteristic (see Tumors of the Lower Jaw, page 316). On radiographic examination, the polycystic type is easily recognized, but this examination alone is not diagnostic because confusion with giant-cell tumor is very possible. A monocystic ameloblastoma is difficult to differentiate from an odontogenic cyst or from a fibro-osteoma. The contour of the ameloblastoma is somewhat lobulated. The dentigerous cyst contains the crown of a tooth pressed away from the alveolar process, while the ameloblastoma may contain a tooth completely surrounded by tumor. Ameloblastomas are treated surgically but the usefulness of adjunctive radiotherapy has been recognized (Quick). They have also been successfully treated by roentgentherapy alone.

A *central fibroma* of the superior maxillary region is a very rare tumor which may arise from retained embryonic connective tissue cells or from perineural or dental follicles (Thomas). It also develops in young individuals very slowly and without pain. Its histologic appearance is characteristic.

*Fibro-osteomas* of the superior maxillary region are generally observed in individuals between 10 and 30 years of age. This disease is often called a localized osteitis fibrosa, but it is not related to the generalized osteitis fibrosa of hyperparathyroid type. It may originate from the peripheral portions of the bones of the face and skull. In the superior maxilla, fibro-osteomas usually appear in the infraorbital region as a small button or mushroom (Billing), but, as they grow, become broad-based (Fig 133). They may invade the entire surface of the maxillary bone and obliterate the sinus. Radiographic examination, however, can show the sinus wall to be displaced without evidence of bone rupture or mucosal swelling. Fibro-osteomas also develop in the man-

As the disease advances, radiographic examination contributes valuable information as to the true extent of the tumor.

Opacity of the ethmoid cells, the frontal sinuses, or even of the opposite maxillary sinus is sometimes observed in carcinomas of the maxillary antrum because of secondary inflammatory complications, but in the immediate vicinity of tumor, these changes may mean neoplastic invasion.

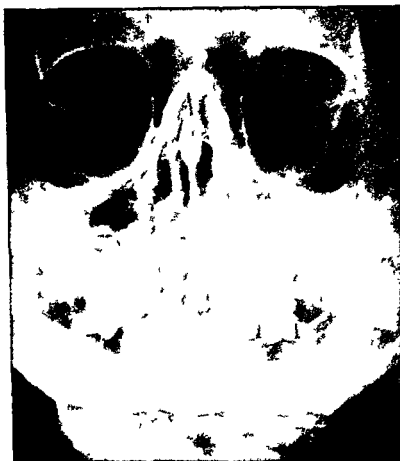


Fig. 132.—Roentgenogram of an early carcinoma of the left maxillary antrum showing cloudiness of the sinus and lower half of the nasal fossa.

**Biopsy**—When the tumor has become ulcerated in the oral cavity, a biopsy specimen can usually be removed with ease for microscopic examination. It is very seldom possible to obtain a biopsy from the nasal fossa. In general the tumor is entirely enclosed and a specimen can only be obtained through an incision. In these cases however, it is preferable to aspirate the tumor through a large needle (see Aspiration Biopsy page 63). This procedure very often suffices for a pathologic diagnosis.

**Differential Diagnosis**—In the differential diagnosis of tumors of the maxillary antrum a variety of conditions have to be considered. *Maxillary sinusitis* seldom produces a tumefaction and its clinical evolution and marked inflammatory elements often facilitate its diagnosis. A variety of rare benign



graphic examination shows a thick shell which may or may not be polycystic. Surgical excision of these tumors is the most widely accepted form of treatment. They are also successfully treated by radiotherapy. Conservative treatment should be given particularly to the tumors in the superior maxilla because most patients are young and the cosmetic result is important. Following the administration of radiotherapy, the tumors regress very slowly over a period of months or even years. Recurrence is characterized by osteolytic thrusts, but these are controllable by a repetition of the treatments. Lacharité reported on a series of eight patients with giant-cell tumors of the superior maxilla who remained well from two to eight years following roentgentherapy. He noted that relatively small doses of radiotherapy resulted in a solid encapsulation, followed by slow regression of the tumor.



FIG. 131. Fibrosarcoma of the superior maxillary region. (Courtesy of Dr. F. Baclesse, Department of Roentgentherapy, Radium Institute of the University of Paris.)

The *mucous* and *salivary gland types* of tumor arise from the mucosa of the maxillary sinus, just as they do from the mucosa of the nasal fossa and oral cavity. Ringertz reported six of his own cases together with nine collected from the literature. The majority of these were found in patients 40 to 59 years of age. The antrum seems to be the most common point of origin of these tumors after the hard palate and the nasal fossa. They have a very slow development, and although the majority of them are benign, some may be malignant and capable of metastasizing (see *Tumors of the Salivary Glands*, page 618). Mucous and salivary gland tumors are well circumscribed and generally encapsulated, and in their expansion destroy but seldom infiltrate the surrounding tissues. They have varied histologic appearances. Surgical excision usually results in permanent cure with the exception of the semimalignant and malignant varieties, which may recur repeatedly following excision.

dible, frontal sinus, and ethmoidal region. The most common of these neoplasms is an entirely chondrified tumor usually called fibro osteoma, but another variety may present more fibrous tissue than bone and for this reason they are called ossifying fibromas. Thomas describes a third variety, the fibro osteoid osteoma which is also poorly calcified. The radiographic examination of these lesions may consequently show varying degrees of calcification but the age of the patient and the painless slow development greatly facilitate the differential diagnosis. Phemister reported thirteen cases of fibro osteoma of the jaw which remained cured from four to ten years after operation.



FIG. 123. Fibro-osteoma of the superior maxillary region developing from the infraorbital region.

*Chondromas* and *myxomas* are rare tumors which may arise from permanent or transitory cartilage. Rickets is an important predisposing factor. They are all observed in young individuals and grow slowly and painlessly, sometimes undergoing calcification. They usually develop from the canine fossa or the molar and palatal processes and are contained in a capsule of connective tissue. These tumors are made up of hyaline cartilage with occasional transition to osteoid or even bony areas and a greater or lesser amount of mucinous material. When the tumors are formed by a synchondrium of cells in abundant mucoid tissue they are usually diagnosed as pure myxomas. Those presenting a comparable amount of mucin and cartilage are often designated as myxoid chondromas. Their blood supply is poor. Radiographically they are transparent and may present spotty calcifications. Treatment by surgical excision is most often successful.

*Basal cell carcinoma* occurs frequently between 10 and 20 years of age. As far as the occurrence in this age group goes, it is reported by Nelson (1934) as being the most common type of cancer. These tumors develop slowly from the epithelium of the upper lip and buccal mucosa again. The radio-

parent tissues (fibrosarcoma). The histologic examination determines the diagnosis of these three varieties. The development of these tumors usually results in pulmonary metastases and death within a period of two years. A wide surgical excision should be attempted when possible. They are radio resistant, however, a few fibrosarcomas are radiosensitive but not radiosurable (Figs 136 and 137). The prognosis is very poor.

*Epidermoid carcinomas of the upper gingiva* may rapidly invade the antrum and reproduce the clinical appearance of an antral carcinoma which has ulcerated the gingiva. In surgical statistics, the former cases are usually associated with carcinomas of the antrum. The differential diagnosis can be made here on the basis of the chronology of the developments. Moreover, carcinomas of the upper gingiva are usually more differentiated, keratinizing carcinomas.

In summary, the differential diagnosis of carcinomas of the maxillary sinus offers little difficulty in the majority of cases. Most benign tumors develop in young individuals in whom carcinomas of the antrum are the exception, the same is true of many of the noncarcinomatous malignant tumors of this area (Ewing's osteogenic sarcoma). The remaining few cases which might be confused are easily diagnosed on biopsy.

### Treatment

**Surgery.** Gensoul in 1826, introduced a radical resection of the superior maxilla as the treatment of malignant tumors of this area (Dechaume). He reasoned "all the procedures practiced to date imply incision in the middle of the cancerous mass and the removal of everything that appears altered but, I ask, who is the surgeon that in this day will dare put in practice such a principle for the cure of cancer of the breast?" The typical operation of Gensoul consists of the total resection of the superior maxilla after severing the natural pedicles: the frontal process of the malar bone, the zygomatic arch, the hard palate at the midline, and the maxilloethmoidal and pterygo-maxillary attachments. Thus the specimen consists of the entire maxillary bone with the antrum, including the floor of the orbit. The procedure usually has to be completed by an exenteration of the orbit. The operation is proper for anatomic amphitheatres, but besides being shocking and disfiguring, it had the disadvantage, in many instances, of removing too much and yet not enough. In spite of a high operative mortality, the operation was successfully practiced during the nineteenth century, but many of the reported cures were giant cell tumors, the benignity of which was not recognized until pointed out by Nélaton (1856). In the beginning of this century, a reaction developed against this classical operation mainly upon the premise stated by Faure that "when the operation is justified it is impracticable and when it is practicable it is unsatisfactory." This opened an era of atypical surgical resections "à la demande" of the lesions (Sebileau, Cornet). These atypical operations had the advantage of a smaller operative mortality but often implied the necessity of removing the tumor by morsels and consequently were frequently followed by recurrences. New, of the Mayo Clinic, reported in 1920 a method of treatment of malignant tumors of the antrum by means of

*Fibrosarcomas* may rarely occur in the superior maxillary region. They are chiefly found in young individuals and apparently arise within the marrow cavity, but tumor tends to extend to involve the cortex and the subperiosteal tissues. They are capable of metastasizing to the lungs, regional lymph nodes and to other bones. Their radiographic appearance is very variable. Roentgenograms often show osteophytic formation which may be mistaken to represent osteogenic sarcoma. The histologic appearance is described in the chapter on Malignant Tumors of Bone, page 972. They are very radiosensitive and thus capable of being sterilized locally if adequate irradiation is administered. Failures of the treatment can most often be charged to the presence of unsuspected distant metastases.



Fig. 14. Maxillary tumor in the superior maxillary region from an individual with carcinoma of the thyroid.

*Sarcomas* of the superior maxilla are very rare and may be observed in the young child as well as in the adult. They may rapidly develop to attain huge dimensions (Fig. 14). Pain is often an early symptom and the rapidity of growth although variable is greater than that of benign tumors. The teeth become loose and may fall spontaneously; paresthesias of the skin and mucous membrane of the mouth may also be present. Innumerable varieties of sarcoma have been described depending on their tissue content, but most of them are of the fibrosarcoma variety. The histologic appearance of the osteogenic sarcoma of the maxilla is similar to the fibrosarcoma of the soft tissue sarcoma of the maxilla. One characteristic may be associated with Paget's disease of the bone. The radiographic examination may prevent or delay or even suggest a correct diagnosis. The tumor may be mistaken for a fibrosarcoma of the soft tissue or a carcinoma of the maxilla. It may be capable of being

logic examination, (2) invasion of the orbit or the temporal fossa, (3) invasion of the skin, (4) invasion of the ethmoid, (5) submaxillary or cervical metastasis

The association of intraorbital curietherapy to surgical removal has been widely accepted as a complementary procedure (New, Denker, Holmgren), but it is doubtful whether the postoperative irradiation contributes any real advantage, it appears certain that the results of the combined procedures depend mainly upon the intelligent choice of patients and the thoroughness of the surgical procedure

These operations most often result in a defect of the hard palate which is easily obturated in most instances by a prosthetic appliance (Martin, Ackerman)



Fig. 138

Fig. 139

Fig. 138—Epidermoid carcinoma of the maxillary antrum developing laterally with invasion of the floor of the orbit and inward displacement of the eye (From del Regato J A Surg Gynec & Obst 1937)

Fig. 139—Same patient seven years following administration of roentgentherapy. Treatments were given in a short time. There was loss of vision in the left eye two years after treatment (From del Regato J A Surg Gynec & Obst 1937)

**ROENTGEN THERAPY**—For a long time, external roentgentherapy was used only as a palliative measure in the treatment of the inoperable carcinomas of the maxillary antrum or for the treatment of postoperative recurrences. Nothing besides alleviation of pain and psychotherapeutic effect was expected. Because the tumor invaded the bone, it was judged futile to try to eradicate the disease by means of external irradiation alone, because a therapeutic dosage would inevitably result in radionecrosis of the bone. A group of ten patients with inoperable carcinomas of the maxillary antrum receiving external roentgentherapy as the only form of treatment was first reported on in 1937 (Regato). This study revealed that patients could be cured with preservation

cautery, and six years later reported ninety seven patients with malignant tumors of the upper jaw treated by surgical diathermy, cautery, and radium. This method of treatment, which started with the soldering iron or "ferrum candens," has evolved into modern electrocoagulation and electrosurgery.

Electrosurgery has been favored for the treatment of malignant tumors of the superior maxillary region because it is devoid of any effect of shock. Holmgren, of Sweden, has been its greatest advocate. The success of the procedure, however, seems to be connected more with its thoroughness than with the particular virtues of coagulation or electrosurgery. Coagulation of the tissues facilitates their removal through an oral opening with, at the most, a small nasolabial incision. The operation is followed by a slow elimination of small fragments of necrotic soft tissues and bone. Holmgren restrains from coagulation near the body of the sphenoid to avoid intracranial complications. Any involved skin is removed and the patient subjected later to plastic repair.



Fig 136



Fig 137

Fig 136 —Postoperative recurrence of a fibrosarcoma of the superior maxilla.

Fig 137 —Same patient following roentgentherapy. The tumor showed surprising radio sensitivity but later recurred.

**CURIETHERAPY** —Hautant and Monod working at the Radium Institute of the University of Paris perfected a technique of open surgical extirpation with the steel knife followed by intracavitary curietherapy. The operation consisted of a wide atypical resection, bordering sometimes into the limits of the Gensoul operation. It was most successful however, when applied to tumors confined to the infrastructure of the maxilla. On the basis of experience, Hautant himself established the following contraindications to this form of treatment: (1) invasion of the pterygomaxillary fossa as revealed by trismus or roentgeno-

of the vision of the eye even when the orbit had been widely invaded by the tumor (Figs 142 and 143), the necessity of protracting the treatment and protecting the lens during part of the treatment was emphasized. These tumors have great radiosensitivity and metastasize late, two qualities which are advantageous for roentgentherapy. Invaded bone recalcifies following irradiation (Figs 140 and 141), although in some instances the elimination of sequestra may result. The protracted administration of roentgentherapy over a period of five to six weeks appears most satisfactory for avoiding untoward effects. Short treatments with a high daily dose may also be successful (Valencia), but the danger of radionecrotic complications of the bone when higher doses are used does not justify its use, and the results are not improved. Successful roentgentherapy of carcinomas of the maxillary antrum requires detailed care and minute evaluation.

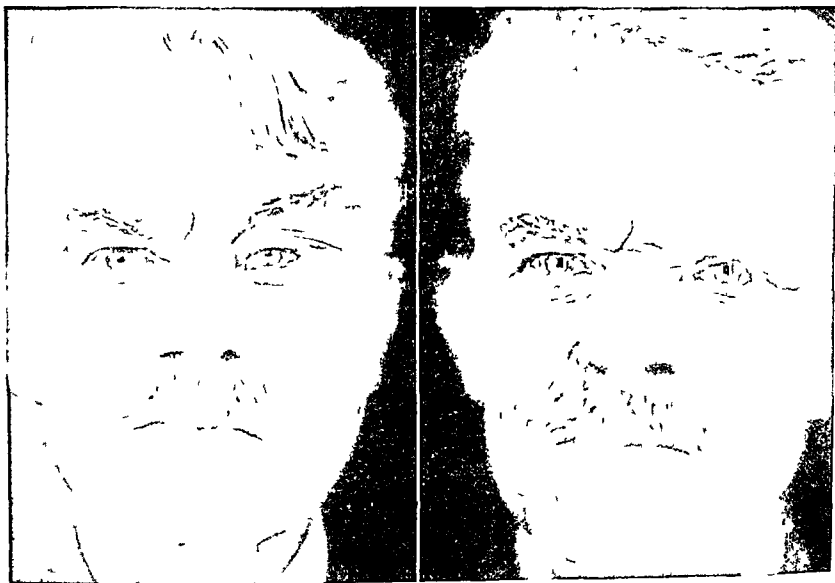


Fig 142

Fig 143

Fig 142—Carcinoma of the maxillary antrum developing in the suprastructure with early invasion of the floor of the orbit and temporal fossa. (From del Regato J. A. Surg. Gynec. & Obst. 1937.)

Fig 143—Same patient five years after administration of roentgentherapy. Treatments were protracted over a period of six weeks and the eye was protected during part of the treatment. The vision was perfect five years after treatment. (From del Regato J. A. Surg. Gynec. & Obst. 1937.)

### Prognosis

Carcinomas of the maxillary antrum which develop in the infrastructure have the best prognosis, but whatever form of treatment is applied, it must be radical. Ohngren reported on forty-five patients with carcinomas of the antrum, fifteen of whom (33 per cent) were living five years or more after treatment. The treatment consisted of electrothermic excisions, electrocoagulation,

Fig 140

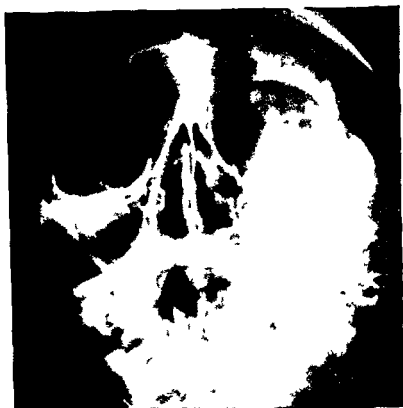


Fig 141

Fig 140—Lateral roentgenogram of patient illustrated in Fig 138. Note the mild destruction of the floor of the orbit and invasion of the inferior orbital foramen.

Fig 141—Lateral roentgenogram of the same patient seven years after administration of roentgenotherapy. Note the elevation of the floor of the orbit at a lower than normal level and the protrusion of the lower lip of the opposite maxillary arch.



## PLATE III

Ulcerating carcinoma of the buccal mucosa at the commissure

Leucoplakia of the buccal mucosa

Ulcerating epidermoid carcinoma of the lower lip invading the buccal commissure

Early epidermoid carcinoma of the floor of the mouth

Generalized gingivitis with profuse bleeding in a case of acute monocytic leucemia  
(Courtesy of Dr H B G Robinson, Ohio State University, College of Dentistry, Columbus, Ohio)

Lapophytic epidermoid carcinoma of the vermilion area of the lower lip

and curietherapy New (1938) reported on a series of ninety one patients with carcinoma of the antrum, of whom thirty (33 per cent) were living without recurrences five years after treatment

Regato reported on ten patients treated with roentgentherapy alone, of whom four remained well five years or longer, all the patients treated could not have been cured by the widest surgical excision

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PLATE III

**Lymphatics**—The lymphatics of the *mucous membrane* of the lip and of the vermillion border gather in three trunks, one medial and two lateral. The medial trunk descends directly to the chin and ends in one of the submental nodes. The lateral trunks follow an oblique direction, cross the lower border of the mandible with the facial vessels, and usually end in one of the prevascular submaxillary nodes. These lymphatics very rarely cross the midline to end in the nodes of the opposite side.

The lymphatics of the *skin* of the lower lip also end in the submental and submaxillary lymph nodes, but the medial lymphatics are richer and often cross the midline to end in the submental and submaxillary lymph nodes of the opposite side (Fig. 145).

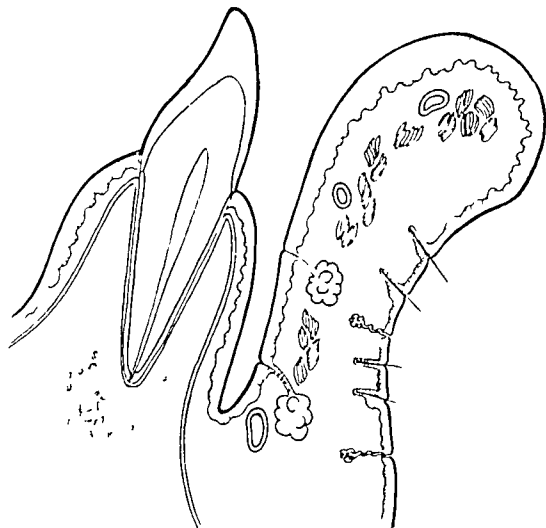


Fig. 144—Submental section of the lower lip

In addition to this classical termination of the lymphatics of the lower lip, it must be noted that in some cases these lymphatics may end in one of the mandibular nodes of the facial group (Rouvière). These nodes are situated just below the subcutaneous tissues of the face, generally along the trajectory of the facial vessels and lateral to the horizontal branch of the mandible. They are not constant.

### Incidence and Etiology

Carcinoma of the lower lip includes lesions which develop on either the mucous membrane or the vermillion area. Carcinomas which develop on the cutaneous aspect of the lower lip, usually basal-cell carcinomas, should be labelled carcinomas of the skin of the lower lip and be considered with other lesions of the skin of the face.

Carcinoma of the lower lip is the most common of all forms of cancer of the oral cavity, representing between 25 and 30 per cent of all these tumors.

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## CANCER OF THE ORAL CAVITY

Malignant tumors of the oral cavity make up about 5 per cent of all forms of cancer occurring in the human body Tumors which develop within the oral cavity present a distinct character, clinical course, are treated differently and have a widely different prognosis depending on their point of origin It is regrettable that the medical literature abounds in therapeutic discussions in which various carcinomas of the oral cavity are considered together as "cancer of the mouth," for it is neither possible nor rational to treat all these tumors as a single unit

In order to understand the behavior of different tumors of the oral cavity and to formulate indications of treatment of the primary lesions and their metastatic adenopathy better, this discussion of cancer of the oral cavity will be divided into the following sections

(1) Carcinoma of the lower lip, (2) carcinoma of the upper lip, (3) carcinoma of the mobile portion of the tongue (anterior two thirds), (4) carcinoma of the floor of the mouth, (5) carcinoma of the buccal mucosa, (6) carcinoma of the upper gingiva (7) carcinoma of the lower gingiva (8) tumors of the hard palate (9) tumors of the lower jaw

## CARCINOMA OF THE LOWER LIP

### Anatomy

The lower lip is a muscular and cutaneous fold which forms the lower half of the anterior wall of the oral cavity and its external opening The lower lip varies considerably in thickness, shape and size, according to the race and age of the individual It extends transversely between the buccal commissures and vertically from its free border to a horizontal depression which separates the lip from the chin The posterior aspect of the lower lip is covered by the same mucous membrane which covers the lower gingiva, reflected upon itself to form the gingivolabial gutter and the posterior aspect of the lower lip This mucous membrane extends to the free border and passes through a gradual transition into the vermilion area of the lower lip The vermilion area is remarkable for its red or pink color It presents thin anteroposterior irregularities on its surface with a moderate depression in the midline The vermilion area ends brusquely on a regular curved distinctive line called the vermilion border which separates it neatly from the skin

The substance of the lower lip is made up of numerous thin muscles, the most important of which is the orbicular muscle (Fig 144)

Of 248 patients with carcinoma of the lower lip admitted to the Ellis Fischel State Cancer Hospital from 1940 to 1946, two-thirds were 60 to 79 years old. Most of these patients were farmers with a long history of outside exposure. Only one eighth of the patients were under 40 years of age (Table IV). Carcinomas of the lower lip are predominantly found in men, in over 600 cases treated at the State Institute for the Study of Malignant Diseases in Buffalo, N. Y., 1926 to 1936, only 27 per cent were found in women (Schreiner). Ahlbom has called attention to the high incidence of carcinoma of the oral cavity, pharynx, and esophagus in Swedish women and its possible relation to the also high incidence of sideropenia (Plummer-Vinson syndrome) found among these patients. Sideropenia is characterized by anemia, achlorhydria, chronic dysphagia and atrophy of the mucous membrane of the mouth and pharynx. The disease is probably due to a dietary deficiency and should be considered a true precancerous condition. It seems to be less prevalent among women with more than average economical standing. This condition accounts for the fact that at the Radiumhemmet in Stockholm more than half of all cases of carcinoma of the lower lip are found in women.

TABLE IV AGE INCIDENCE OF 248 CASES OF CARCINOMA OF LOWER LIP\*  
(PATIENTS PREDOMINANTLY FROM RURAL AREAS)

AGE GROUP	NUMBER OF CASES	PERCENTAGE	FRACTION OF TOTAL
25-29	3	1	1/8
30-39	16	6	
40-49	12	5	
50-59	17	19	
60-69	63	25	2/3
70-79	76	30	
80-89	27	11	
90-94	4	2	
Total	248	99	

\*Note the small proportion of patients under 50 years of age.

Carcinoma of the lower lip is very rare in Negroes, who are not immune to other forms of cancer of the oral cavity. Only one case of carcinoma of the lower lip was observed at the Homer Phillips Hospital for Negroes, St. Louis, in a period of ten years (Smiley).

Tobacco, and in particular the habit of pipe smoking, has been considered responsible for the development of carcinoma of the lower lip, which is often referred to as "cancer of pipe smokers." The assumption that the heat of the pipe stem habitually applied to the same side of the lower lip over a period of years may end in the production of carcinoma is as well established in the medical profession as in the lay public, yet carcinoma of the upper lip is very infrequently observed. It is also argued that the porous clay pipes and the wooden stems permit seepage of tarry products which come in direct contact with the lower lip on the dependent side of the pipe stem. However, the infrequent occurrence of carcinomas of the upper lip which is equally affected by the heat of the pipe stem, the not infrequent occurrence of carcinoma of the lower lip toward the midline and its rather infrequent occurrence at the buccal commissure where most pipe smokers hold the stem should be



Fig 14c.—Anatomic sketch of the lymphatics of the lower lip ending in the submental and prevascular submaxillary lymph nodes but sometimes stopping in the facial nodes. The lymphatics of the skin of the lower lip (dotted line) may cross the midline to end in submental and submaxillary nodes of the opposite side.



of the vermilion border which immediately creates a defect (Fig 148), while the tumefaction itself is limited to the area immediately surrounding it. These lesions are slower in their development but usually infiltrate the entire depth of the lip (Fig 149). The verrucous type usually extends toward the cutaneous side of the lower lip (Fig 158). It has a very irregular surface and appears to be ulcerated only in the crevices. It develops very slowly, may involve the entire width of the lip, and may even extend to the chin. The verrucous type, however, has little tendency to extend to the mucous membrane aspect of the lower lip or to infiltrate in depth.

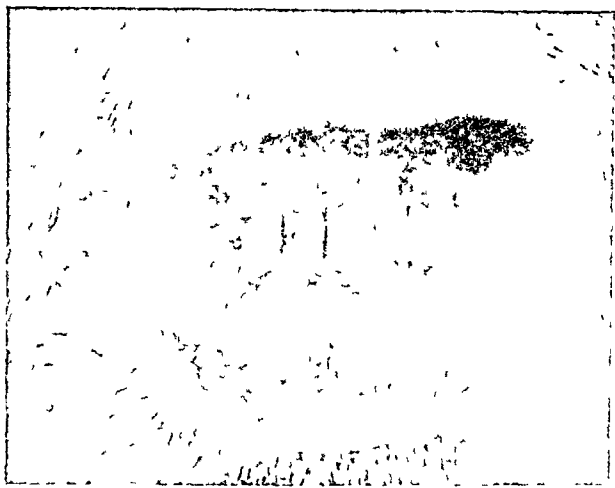


Fig 146—Superficially ulcerating epidermoid carcinoma of the lower lip. This lesion is usually preceded by a blister.

**METASTATIC SPREAD**—Metastases from carcinoma of the lower lip do not occur as early or as frequently as in other forms of cancer of the oral cavity. In many instances a metastasis never occurs in spite of very extensive development of the primary lesion (Fig 150). The most commonly invaded nodes are those of the submaxillary region on the same side as the lesion. The lesions of the middle third of the lower lip may metastasize to the submental nodes, but they do this rather infrequently. In extensive lesions or in rapidly growing undifferentiated tumors, a node may infrequently be found attached to the external aspect of the horizontal branch of the mandible (Fig 151). Involvement of cervical nodes is found in about 12 per cent of the cases with submaxillary metastasis (Eckert) but seldom occurs in the absence of submaxillary metastases. Metastases to the opposite side of the neck are seldom observed unless the lesion has invaded near or beyond the midline (Figs 164 and 165). When the lesions have ulcerated the skin, contralateral metastases are more frequent. Distant metastases have rarely been observed. Braund reported that in thirteen cases of cancer of the lower lip which came to

sufficient evidence to eliminate this argument. In addition, among patients with carcinoma of the lower lip pipe smokers constitute a minority.

Leucoplakia is not uncommon in the lower lip. Schreiner found leucoplakia accompanying carcinoma of the lower lip in 26 per cent of his cases while Martin found it in 28 per cent. In general, the leucoplakia is superficial and shows little change throughout the years. Less often it will become thickened, indurated and secondarily infected. The coexistence of syphilis with carcinoma of the lower lip is not as frequent as with other carcinomas of the oral cavity, it has been variously reported between 36 per cent (Schreiner) and 10 per cent (Martin).

Long standing exposure to sunshine, wind and frost (farmers, sailors, etc.) is by far the most frequent cause of carcinoma of the lower lip. Chronic exposure to sunshine over a period of fifteen to thirty years results in dryness and hyperkeratosis of the skin of the face and neck as well as of the exposed aspect of the lower lip. This hyperkeratosis gradually develops into a superficial area of ulceration which later becomes indurated and is found to be carcinomatous. The carcinogenic action of the solar rays is very variable and requires a different intensity and length of exposure according to the individual. In general, blonde skinned individuals are more easily affected.

Carcinomas of the lower lip, however, are also observed in individuals who have never been exposed to prolonged effects of sunlight. If separate statistics should be drawn on outdoor and indoor workers with carcinoma of the lower lip, it might well be found that in the outdoor group the lesions develop on older patients usually giving a history of long standing hyperkeratosis, while in the indoor group the lesions would more often develop from normal lip or from leucoplakia in younger individuals frequently giving a history of syphilis. Such a division may explain the discrepancy in the incidence of leucoplakia and syphilis, for it may depend on the proportion of rural or urban patients reported.

### Pathology

**Gross Pathology**—Most carcinomas of the lower lip develop on the portion of the vermilion border which lies outside of the line of contact with the upper lip at a point equally distant from the midline and buccal commissure (Figs 146, 147 and 148). They may develop in the middle third of the lower lip and less frequently may start at the buccal commissure (Fig 162). In general carcinoma develops on a long standing hyperkeratotic lesion, but those which develop on the buccal commissure or toward the inner aspect of the lower lip may do so on the basis of a pre-existing leucoplakia.

There are three distinct types of carcinoma of the lower lip: exophytic, ulcerating and verrucous. The majority of these lesions are of the exophytic type (Fig 152). The lip becomes thickened and induration may involve an entire half of the lower lip, while the ulceration is limited to the vermilion border and is comparatively small. These lesions may become bulky and in later stages may present spontaneous necrosis with loss of substance. The ulcerating form of carcinoma of the lower lip usually starts with an ulceration

The well-differentiated carcinomas (Grade I) usually include a group of papillary lesions which we call verrucous carcinomas and which arise also from other areas of the oral cavity. These tumors have been variously referred to by different authors, but no effort has been made to individualize them as a clinicopathologic entity.

Basal-cell carcinomas do not arise on the mucous membrane or vermilion area of the lip. However, these lesions, having arisen on the skin of the lower lip, may invade this area secondarily. Such cases should be considered as carcinomas of the skin.

### Clinical Evolution

The most important single detail in the history of patients with carcinoma of the lower lip is the description of the onset on the basis of a "blister." This blister evidently precedes the development of a superficial ulceration (Fig. 146). In many other cases there is a history of recurrent scabs which finally leave a superficial bleeding ulceration. This process may last many years and this explains some of the unusually long histories. In other instances the carcinoma develops on a known area of leucoplakia, and it is seldom that a carcinoma develops from an entirely normal lower lip.

In general, the development of a carcinoma of the lower lip is rather slow and produces no symptoms until it has reached a rather advanced stage. It is not infrequent that these lesions be ignored for years before advice is sought (Fig. 149).

The occurrence of an adenopathy is very variable in carcinomas of the lower lip. In general, as many as 20 per cent of the patients apply for treatment after metastases have already developed. If the primary lesion has been controlled, however, relatively few patients will ever develop a metastasis. In a series of 223 patients with carcinoma of the lower lip without apparent metastases, only twenty-seven (12 per cent) developed metastases after treatment of the primary lesion (Martin). In our hospital only 6 per cent of the patients applying for treatment presented evident metastases, and only 6 per cent of those apparently without metastases developed one after treatment of the primary lesion (Table VI). It should be recognized that the presence of a palpable adenopathy in the submaxillary region is not always evidence of metastatic disease, for most normal adults have enlarged submaxillary lymph nodes. In addition, tumors of the lower lip are usually secondarily infected or associated with poor oral hygiene. Lymph nodes measuring under 2 cm. in diameter may or may not be metastatic, but if the nodes become larger, the chances of their being involved are considerably greater (Taylor and Nathanson). Because of this, the usual comment in the literature about patients "with palpable lymph nodes" may be misleading. The division of carcinoma of the lower lip into two groups, with or without "palpable lymph nodes," actually is more often meant to imply with or without "clinical evidence of metastases." Obviously, the clinical assumption of metastases should always be substantiated by pathologic examination of metastases biopsy or of the surgical specimen.

autopsy, there were only two instances of distant metastases. Submaxillary and facial nodes may rapidly become adherent to the mandible and in later stages may ulcerate the skin. When nodes are present when the patient is first seen, the chances are that more than one node is involved.

The likelihood of the production of metastases increases with the duration of the primary lesion and also with the increase of its dimensions. However, attempts made to correlate the increasing percentage of metastases with the duration or enlargement of the primary lesion usually show that although



Fig. 147—Squamous carcinoma of the lower lip with central ulceration and rolled border.



Fig. 148—Ulcerating carcinoma of the lower lip with diffuse infiltration.

there is a definite up trend it is also true that very large and long standing lesions may indeed show a lesser incidence of metastases. This is probably due to the fact that verrucous carcinomas which form the majority of this last group are tumors with a remarkable local malignancy which never metastasize. If the verrucous type of carcinoma could be eliminated there would be a much better correlation of increased incidence of metastases with increase in size and duration of the primary lesion.

The chance of metastases also increases the less differentiated the carcinoma. Taylor and Nathanson reported only a 6 per cent incidence of metas-

## Treatment

The medical literature abounds in controversial statements as to treatment of carcinoma of the lower lip and its metastases

**Treatment of the Primary Lesion**—It is generally admitted that skillful surgical excision, roentgentherapy, or curietherapy may contribute a high percentage of local cures in carcinoma of the lower lip. But while some authors readily acknowledge that radiotherapy offers a better aesthetic result, others assert that in this respect surgery is the method of choice. These differences of opinion are not explained on the basis of varied surgical techniques, but rather on the basis of a very unequal variety of radiotherapeutic skills and experiences



Fig. 152



Fig. 153

Fig. 152—Exophytic carcinoma of the vermilion border of the lower lip

Fig. 153—Same patient five years after surface application of curietherapy. Note good aesthetic result. (Courtesy of Dr. J. P. Eberhard, Jefferson Medical College, Philadelphia, Pa.)

**CURIETHERAPY**—Interstitial application of radium element needles or "radon seeds" has been now almost universally abandoned as a method of treatment of primary carcinomas of the lower lip. This form of treatment results in marked fibrosis and atrophy with obvious asymmetry and deformity. In addition, carcinomas of the lower lip are mostly of the exophytic rather than the infiltrating type and consequently do not require a high concentration of radiations for local sterilization. Superficial applications of radium element needles or radon tubes is a satisfactory method of treatment which is still rather widely used. The radium can be supported by a specially molded apparatus rolled around the lip and fixed to the chin. Colombia paste, which can be molded at a temperature not burning to the skin and which does not melt at body temperature, is used with advantage for this purpose (Esguerra). Temporary prosthesis to be held between the gums can also be used. This form of application results in a rather homogeneous crossfiring of the affected area. When radium element is used, this procedure has the

TABLE VI METASTASIS IN 248 PATIENTS WITH PATHOLOGICALLY VERIFIED CARCINOMAS OF LOWER LIP ADMITTED TO ELLIS FISCHER STATE CANCER HOSPITAL DURING ITS FIRST SIX YEARS (PATIENTS FOLLOWED FROM ONE TO SEVEN YEARS)

	TOTAL NUMBER OF PATIENTS	WITH METASTASES ON ADMISSION	APPARENT LY WITH OUT ME TASTASES ON AD MISSION	METASTASES BECAME EVIDENT AFTER TREATMENT OF LIP
Without previous treatment	194	7 (4%)	187	11 (6%)
With previous inadequate treatment	54	8 (15%)	46	3 (6%)
Total	248	15 (6%)	233	14 (6%)

### Diagnosis

Although most carcinomas of the lower lip can be easily recognized clinically, some of the early lesions arising from an area of hyperkeratosis and presenting only superficial ulceration may not be clinically evident and can only be diagnosed by biopsy. The same applies when a carcinoma arises from a long standing patch of leucoplakia which has become ulcerated or thickened.

The biopsy specimen of lesions of the lower lip should be obtained with a scalpel, should be sufficiently deep, and should include a part of the surrounding normal skin. In the case of verrucous carcinoma, particularly, superficial biopsies may show nothing but hyperkeratinization and chronic inflammation. If the clinical impression suggests malignant disease, renewed biopsies should be taken sufficiently deep from the borders of the lesion.

As it has been noted, nothing can be concluded as to the presence of metastases when nodes which are less than 2 cm in diameter are felt in the submaxillary region. A positive aspiration biopsy in such cases will be of value in deciding the course of treatment.

**Differential Diagnosis**—Because so often a carcinoma of the lower lip arises from a vesicle herpes may be mistaken for cancer. Long standing hemangiomas which are usually accompanied by other similar lesions of the oral cavity may bleed or become infected. The differential diagnosis in such cases may be simplified by noting the characteristic bluish appearance of the hemangiomas and their exceptionally long history. Cheilitis due to vitamin B deficiency is never accompanied by induration and appears at the buccal commissure on both sides. A syphilitic chancre usually has an indurated border but a clean regular base does not grow over 1.5 cm in diameter, and is rare on the lower lip.

The main challenge in the differential diagnosis comes with the lesions such as hyperkeratosis and leucoplakia which are known to precede carcinoma. Repeated observation may be necessary. In the meantime, the patient may be advised as to improvement of oral hygiene, extraction of teeth, elimination of use of tobacco, and local application of petroleum jelly. If there is no spontaneous improvement under this treatment, there should be no further hesitation in removing a specimen for microscopic diagnosis.

tumor. In the proper evaluation of all these factors and their wise application, there is no room for amateur radiotherapists.

External roentgentherapy is capable of sterilizing with greater certainty small and large tumors of the lower lip. In addition, the proficiency of its adaption to the particular circumstances of the case contributes to obtain the best aesthetic results (Figs. 155, 157, and 161).

Fig. 156

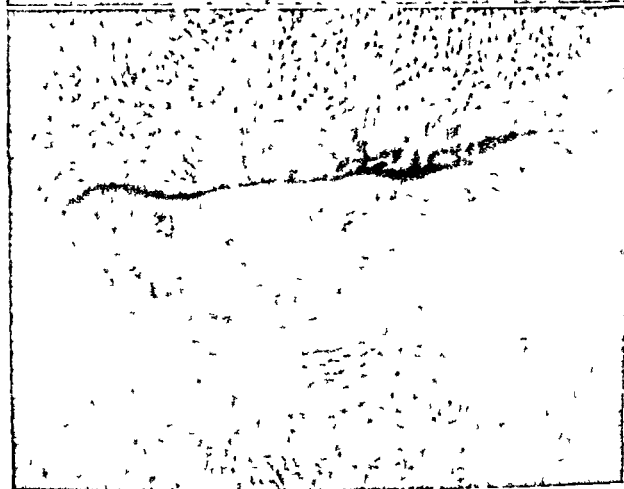
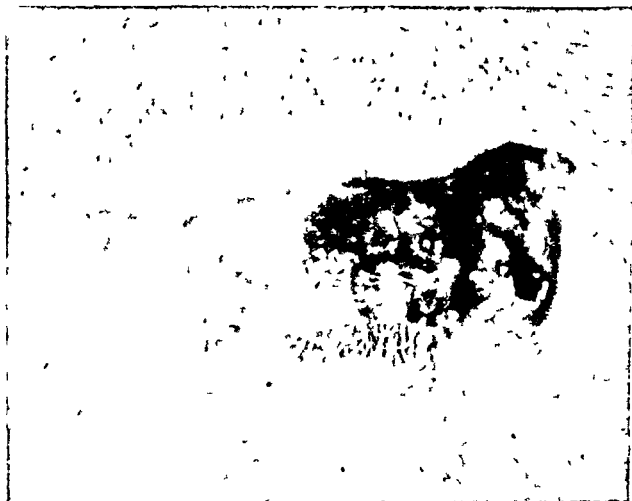


Fig. 157

Fig. 156—Carcinoma of the entire half of the lower lip

Fig. 157—Same patient five years after roentgentherapy. Note absence of atrophy or telangiectasis.

advantage of possibly being applied during a limited part of the hours of the day, allowing a protraction of the treatment in time (between ten and fourteen days) and resulting in considerably better aesthetic result than continuous application (Fig 153). Furthermore, interrupted applications allow treatment without hospitalization. Superficial curietherapy requires considerable time, attention and skill and, in addition, is seldom successful on the large tumors with widespread superficial ulcerations. With bulky lesions, the necessary readjustments of the apparatus as the diseased area shrinks become disheartening.



Fig 154

Fig 155

Fig 154.—Carcinoma of the lower lip extending over two thirds of its length.

Fig 155.—Same patient three years following roentgentherapy. The only defect is that due to destruction by the tumor. Treatments were protracted over five weeks.

**ROENTGENTHERAPY**—External roentgentherapy is a considerably more satisfactory means of treatment than surface curietherapy. Whether the lesions are small or extensive, whether they are exophytic or excavating, roentgentherapy can definitely cure the overwhelming majority of carcinomas of the lower lip and contributes the best aesthetic results. Good results are not possible, however, by routine application of roentgentherapy with fixed factors of quality of radiation as well as of daily and total dosage and total duration of treatment. Intelligent variations of the quality of radiation used (100 to 200 kv, 3 mm of aluminum to 2 mm of copper filtration) depending on the extension and on the infiltrating quality of the tumor, will determine the outcome. There is also need for an intelligent protraction of the treatments (one week to six weeks) and of the total dosage (3,000 to 6,000 roentgens measured at the surface) depending on the character and extension of the



sliding of the soft tissues of the cheek without great disproportion in the length of the lips or the tension exerted upon them. This type of operation provides a lower lip which shields the teeth, allows an intelligible speech, and insures against drooling but lacks in mobility and eventually becomes thinner. Another form of cheiloplasty introduced by Estlander, in 1865, consists of repairing the defect of a V-shaped excision of the lower lip by a flap of the

Fig 160

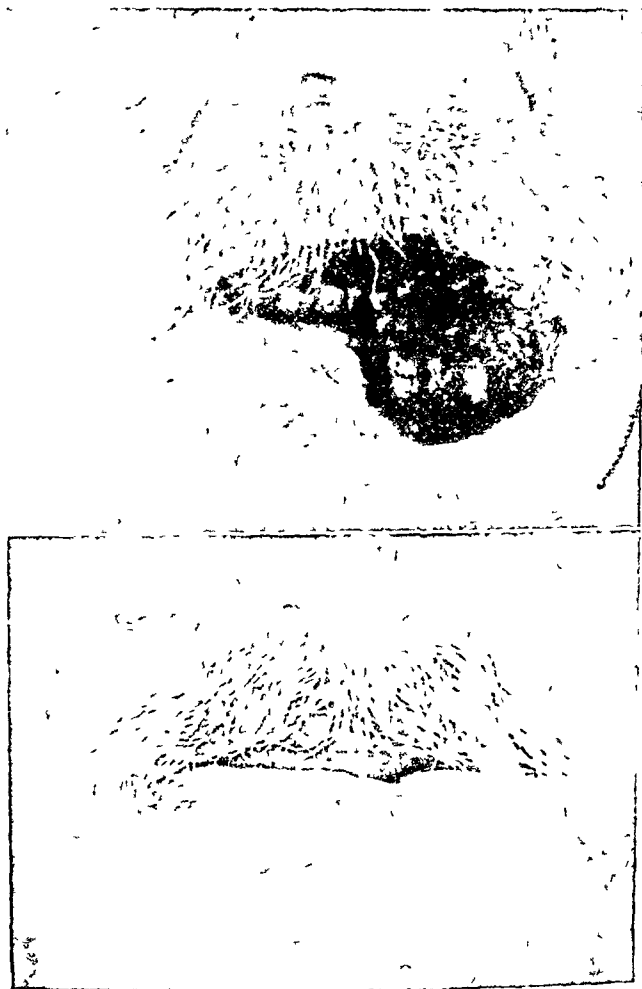


Fig 161

Fig 160 —Extensive exophytic carcinoma of the lower lip  
 Fig. 161 —Same patient five years after roentgentherapy (Courtesy of Dr. T. P. Fisher)  
 hard Jefferson Medical College Philadelphia Pa.)

**SURGERY**—The V shaped excision is the simplest form of surgical treatment of carcinoma of the lower lip. It is a minor procedure which can be done under local anesthesia and does not require hospitalization. A wedge shaped section of the entire thickness of the lower lip is removed, allowing a margin of at least 0.5 cm. beyond the recognized limits of the tumor. This operation implies only a diminution in the length of the lower lip with consequent decrease in the size of the oral opening. The excision of small lesions from rather large mouths may result in a satisfactory aesthetic result if care is exercised in the approximation of the margins after removal. With small mouths and thin lower lips, however, the most limited excision results in constricted oral openings which may interfere with speech or the introduction of a dental appliance. For this reason, a V shaped excision should be done only in patients with large mouths and thick lower lips. Other forms of local excision leaving an elliptic defect give an undesirable aesthetic result and offer no additional advantage.



Fig 158

Fig 158—Verrucous carcinoma of the lower lip extending to the skin.



Fig 159

Fig 159—Same patient following roentgentherapy.

When surgical treatment is contemplated for lesions which will require an excision of more than one fourth of the entire length of the lower lip a V excision becomes unsatisfactory and some form of cheiloplasty has to be considered.

The oldest means of immediate repair of a defect of the lower lip caused by surgical excision is a sliding of the soft tissues of the cheek toward the anterior midline. Such a procedure is greatly helped by an artifice introduced by Bernard in 1853, consisting of the extirpation of two triangular shaped portions of the upper lip and nasolabial fold permitting a more satisfactory

excision of the affected tissues and to repair the defect by a pedicle graft (Figs 169 and 170). Most of these cases require additional surgical management of a submaxillary adenopathy, but the long surgical procedures, tedious as they may be, are well justified (Figs 171 and 172).

Fig 164



Fig 165

Fig 164—Exophytic carcinoma of the midline of the lower lip

Fig 165—Same patient six months after roentgentherapy. Bilateral submaxillary metastases had developed rapidly.

To summarize, roentgentherapy is the treatment of choice of carcinoma of the lower lip, but in certain specified instances surgical treatment may be preferable.

1 With a small lesion and a large mouth, local surgical excision gives enough assurance of control and satisfactory aesthetic results and is, in addition, more expeditious.

same shape taken from the upper lip, rotated downward to form a new buccal commissure, and maintaining, at the same time a circulation through the coronary artery of the lip (Fig. 168). Such form of cheiloplasty is best suited for excisions of lesions of the lateral third of the lower lip. The operation results in a definite asymmetry which, with time, may become less noticeable but which is at best undesirable (Fig. 167).

In the surgical treatment of extensive lesions of the lower lip, particularly those which may extend to the cheek, it may be preferable to do a wide

Fig. 167



Fig. 168

Fig. 167—Ulcerating carcinoma of the lower lip near the buccal commissure

Fig. 168—Same patient four years after roentgentherapy. The atrophy, retraction and undesirable result are due to intensive treatment given in a short time.

4 When there has been previous inadequate radiotherapy with marked and extensive changes of the surrounding areas, further radiotherapy may be contraindicated and cheiloplasty preferable

5 When radiotherapeutic skill is not available, a surgical procedure is obviously indicated

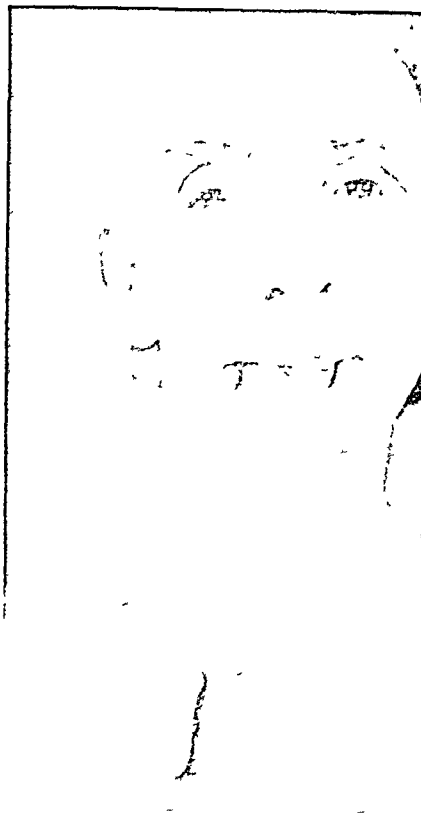


Fig. 169

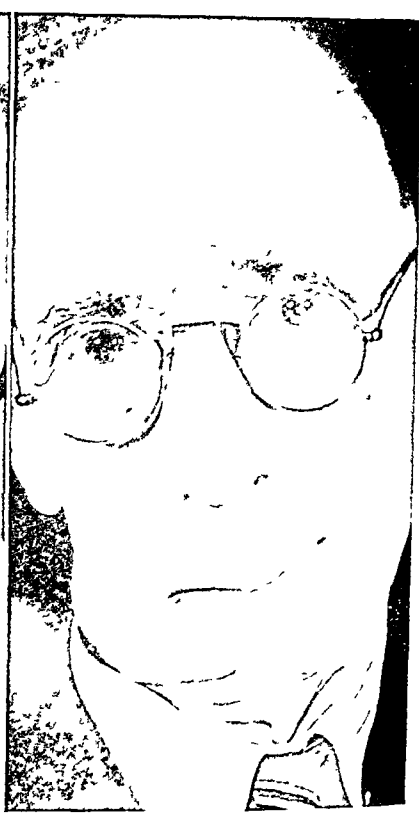


Fig. 170

Fig. 169—Defect left by wide excision of a carcinoma of the lower lip

Fig. 170—Excellent result following plastic repair by a pedicle graft (Courtesy of Dr. Eugene Bricker, Department of Surgery, Washington University School of Medicine, St. Louis, Mo.)

**Treatment of the Submaxillary Metastases**—Patients with carcinoma of the lip who present a metastatic adenopathy should be treated by a neck dissection. In some instances, as a second choice procedure, radiotherapy may be considered.

**RADIOTHERAPY**—External roentgentherapy is capable of sterilizing metastatic carcinoma from a primary lesion of the lower lip, but this form of

2 With very extensive lesions, a good aesthetic result may not be possible with roentgentherapy because of the resulting defect. This may require plastic repair by means of tubed flaps. In such instances surgical treatment might be more satisfactory from the start.



Fig 166



Fig 167

Fig 166—Extensive carcinoma of the lower lip which had already metastasized to the submaxillary lymph nodes.

Fig 167—Same patient following an Estlander operation which was done in order to facilitate immediate performance of a neck dissection.



Fig 168—Estlander operation for carcinoma of the lower lip. The defect of a V excision is filled by a flap from the upper lip.

3 With small or moderately large lesions which have already metastasized the surgical management of the primary lesion will allow immediate care of the adenopathy.

Fig 173



Fig 174

Fig. 173—Metastatic carcinoma of the submaxillary region from a surgically excised primary lesion of the lower lip. The metastatic nodes were adherent to the mandible (From Sugarbaker E D and Gilford J Surg Gynec & Obst, 1916)

Fig 174—Same patient following combined jaw resection and neck dissection. The patient has remained free of disease three years following treatment

treatment requires several weeks and causes the development of extensive mucous membrane and skin reactions which are not justified if a neck dissection is practicable. When a neck dissection is contraindicated, particularly in the presence of an undifferentiated tumor, a thorough roentgentherapy is then indicated.

Fig 171

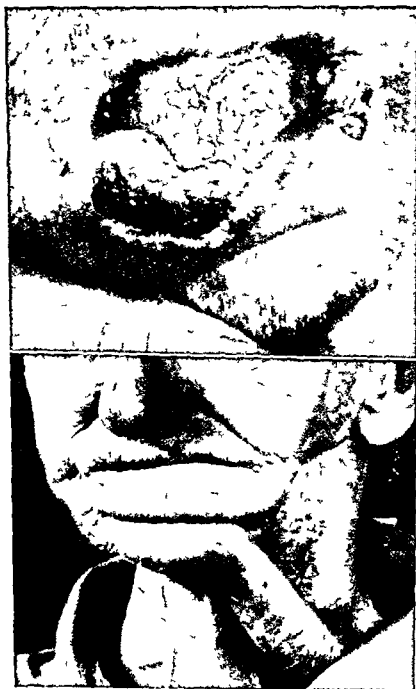


Fig 172

Fig 171 —Extensive recurrent carcinoma of the lower lip following inadequate treatment and presenting submaxillary metastases

Fig 172 —Same patient following wide local excision, neck dissection and plastic repair by means of tube flaps



When a metastasis is present on initial examination, the chance of survival after treatment of the primary lesion and the metastatic nodes is lower than just mentioned (but better than that of other lesions of the oral cavity presenting metastases). Martin reported on a series of ninety patients with carcinoma of the lower lip with accompanying metastases, of whom twenty-two (24 per cent) were living and well five years after treatment. Baud reported on a series of forty-four patients surgically treated for metastatic carcinoma from the lower lip, fourteen patients (32 per cent) were well five years or longer after the operation. The presence of bilateral metastases further diminishes the percentage of cures, but these are still rather good. Taylor and Nathanson collected twenty-six cases with bilateral metastases, in which five patients (20 per cent) were cured after surgical treatment.

Attempts to remove submaxillary lymph nodes, even when they have become adherent to the skin or to the mandible, will yield a good percentage of results although at the expense of some permanent deformity and a higher operative mortality (Sugarbaker).

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Interstitial implantation of radon seeds has been used as a complement of external irradiation. Such a procedure lacks in the precision required for the sterilization of a node. If the nodes are to be treated by radiotherapy a thorough external irradiation is preferable.

**SURGERY**—In establishing indications for a neck dissection, Duffy stipulated the following conditions: (1) the primary lesion should be controlled, (2) the primary lesion should be limited to one side of the mouth, (3) the carcinoma should show marked histologic differentiation, (4) the metastases must be limited to one group of nodes in two contiguous cervical triangles, (5) the carcinoma must not have perforated the capsule of the lymph nodes, (6) there must not be an adenopathy on the opposite side, (7) there must not be a distant metastasis, and (8) the patient should be in good general condition.

When applying these criteria to the treatment of metastatic adenopathies from the lower lip, there are more exceptions than compliance to these rules. The metastases from a carcinoma of the lower lip are highly curable, and enlarged operations are justified in these patients where they would not be warranted in the treatment of other metastatic adenopathies. No treatment of a metastatic adenopathy should be undertaken unless the primary lesion has been or is assumed to be controlled. If the primary lesion has extended beyond the midline and there is no palpable adenopathy on the opposite side, the neck dissection should be extended merely to include a "prophylactic submaxillary dissection" of the opposite side.

As a rule, carcinomas of the lower lip are moderately differentiated. In the rare occasions when they are highly undifferentiated and rapidly growing a neck dissection may have little chance of success, but the attempt is nevertheless justified if the metastasis appears localized to the submaxillary region. The presence of metastases in two contiguous cervical triangles may sometimes, but not always, be a justifiable contraindication of a neck dissection for it is only in very advanced cases that the nodes of the upper cervical region appear involved. Invasion of the lymph node capsule by tumor implies the adhesion of the node and invasion of neighboring structures, but this is not a contraindication to a therapeutic neck dissection in the treatment of metastatic carcinoma of the lower lip (Sugarbaker 1945). The excision of parts of the invaded mandible in the same block with the submaxillary contents often brings about a permanent cure (Figs 173 and 174). Furthermore, the presence of metastases on the opposite side of the neck is not, in itself, a contraindication to surgical treatment of metastatic adenopathies. Bilateral neck dissections which imply ligation of both internal jugular veins have been performed successfully by skillful surgeons (Leclerc, Tailhefer, Fischel).

Because carcinomas of the lower lip always metastasize first to the submaxillary region and because invasion of upper cervical lymph nodes usually follows, a compromise in the procedure of the neck dissection may be applied in these cases. It is generally conceded that a partial upper neck dissection (suprathyoid) is usually satisfactory, but if there are palpable upper cervical lymph nodes, a radical neck dissection is more satisfactory. On the other hand, an enlargement of the operation to include extirpation of half of

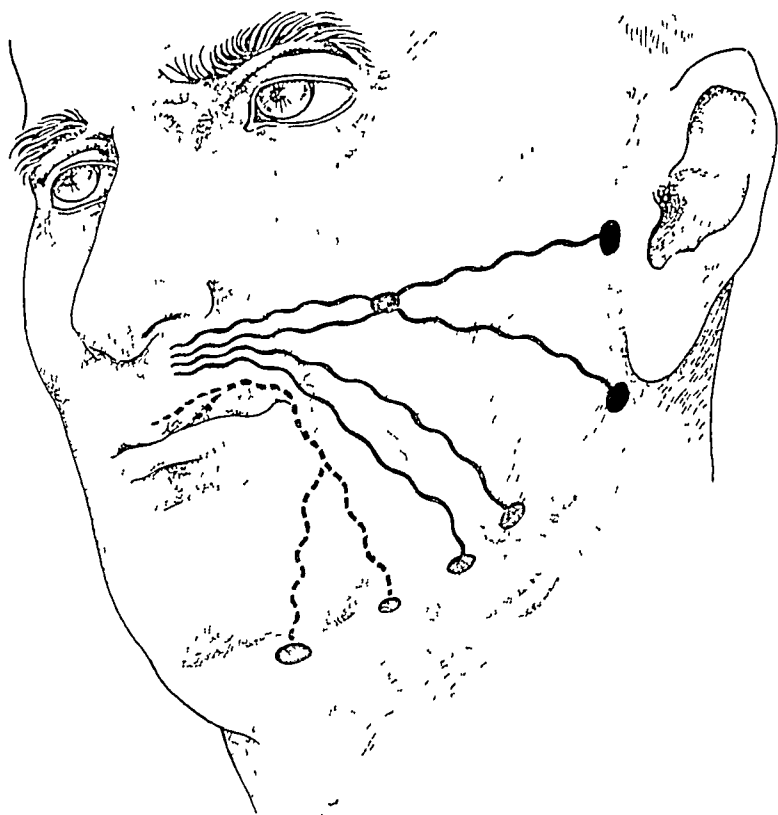


FIG. 176.—Anatomic sketch of the lymphatics of the upper lip which lead to the buccal nodes, parotid and upper cervical lymph nodes as well as to the pre- and retrovascular submaxillary lymph nodes. The lymphatics of the skin of the upper lip (dotted line) may cross the midline to terminate in the submental and submaxillary nodes of the opposite side.

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## CARCINOMA OF THE UPPER LIP

### Anatomy

The upper lip is a muscular and cutaneous fold which forms the upper half of the anterior wall of the oral cavity and its external opening. It varies considerably in shape according to the race and age of the individual. Transversely it extends from the buccal commissures, vertically, from the free

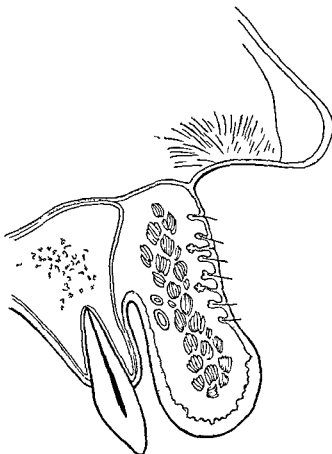


Fig. 17a.—Anatomic sketch of the upper lip in sagittal section

border to the base of the nose in the center and to the nasolabial folds on each side. The mucous membrane which covers the upper gingiva reflects upon itself to form the gingivolabial gutter and the posterior aspect of the upper lip, and as it extends to the free border it passes through a gradual transition

### Clinical Evolution and Diagnosis

As a general rule a carcinoma of the upper lip grows more rapidly than its counterpart on the lower lip. As a rule it is exophytic and superficially ulcerated. The differential diagnosis with salivary gland tumors is easily

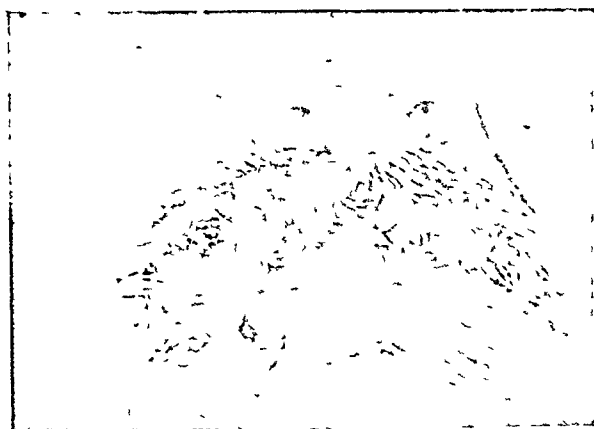


FIG. 177—A carcinoma of the upper lip of the verrucous type with extensive ulceration of the skin.



FIG. 178—Histological section of the upper lip in a case of Noma.

made on the basis of the great difference in their speed of development and time of evolution and on the fact that salivary gland tumors are not ulcerated. Their histology is characteristic (see Salivary Gland Tumors page 618). The

into the vermillion area of the upper lip. The vermillion area is remarkable for its red or pink color. It ends brusquely in a regular curved line which separates it neatly from the skin. The substance of the upper lip is formed by numerous thin muscles, the most important of which is the orbicular muscle.

**Lymphatics**—The lymphatics of the upper lip are more numerous than those of the lower lip. Those of the mucous membrane may gather into five trunks which end in the preauricular nodes of the parotid in the upper cervical nodes just below the parotid in the pre and retroauricular submaxillary nodes, and in the submental nodes. Occasionally a small number of these lymphatic trunks end in the buccinator group of facial nodes which are always found outside of the buccinator muscle and its fascia and above a line extending from the buccal commissure to the lobule of the ear. The lymphatics of the skin of the upper lip follow a similar course to those of the mucous membrane, but some of the lymphatics of the skin may cross the midline to end in the submental and submaxillary lymph nodes of the opposite side (Fig. 176).

### Incidence and Etiology

Carcinomas of the upper lip occur considerably less often than those of the lower lip. Although Schreiner found 22 cases in 619 carcinomas of the lips a greater proportion of cases has sometimes been found. There seems to be a greater proportion of women with carcinoma of the upper lip than with carcinoma of the lower lip.

Perhaps the low incidence of carcinoma of the upper lip is the best argument against the possible causative effect of tobacco, and particularly pipe smoking in the production of these tumors. The upper lip is, however, better protected against the action of irritants.

### Pathology

**Gross and Microscopic Pathology**—Carcinoma of the upper lip may appear in the form of an exophytic growth rather frequently near the midline. In some cases the tumor is barely or not at all ulcerated and it infiltrates the entire thickness of the lip. Some lesions are verrucous and rather superficial.

The majority of tumors of the upper lip are epidermoid carcinomas, but it should be borne in mind that these may sometimes appear as spindle cell carcinomas which may be confused with other tumors (Martin). Tumors of mucous and salivary gland type may also develop in the upper lip. These tumors are usually benign but present a variety of appearances which may make the pathologic diagnosis difficult, particularly as this type of lesion is not common. Salivary gland tumors are more frequently found (9 to 1) in the upper than in the lower lip (Teggers). Basal cell carcinomas reported in this area originate in the skin of the upper lip (Figs. 180 and 181).

**METASTATIC SPREAD**—Metastases from a carcinoma of the upper lip may go directly to the upper cervical region and to the preauricular nodes of the parotid as well as to the submaxillary region. The metastases are usually widespread in these areas. Martin reported twenty-one cases, ten of which (48 per cent) eventually metastasized.

spindle type of epidermoid carcinoma also has little tendency to ulcerate. Carcinomas of the upper lip metastasize earlier and more frequently than those of the lower lip. Hemangiomas occur in the upper lip but offer no difficulty in diagnosis.

### Treatment

Carcinomas of the upper lip may be treated successfully by any form of radiation therapy. However, tumors of the spindle-cell type and salivary gland tumors are best treated by a surgical excision. In such instances, an Estlander operation is indicated. This consists of a triangular-shaped excision to be filled with an identical flap from the corresponding part of the lower lip which is turned around a thin pedicle to form a new buccal commissure (Fig. 179).

### Prognosis

It is admitted that the prognosis of carcinomas of the upper lip is not as good as that of carcinomas of the lower lip. Ecker reported on twelve patients treated surgically, six of whom survived five years, and six treated by curietherapy, three of whom survived five years. Martin reported 41 per cent five-year survival in his group of twenty-one patients. Of ten patients who had metastases, seven did not survive. The time of survival of those who were unsuccessfully treated was twenty-one months as compared with forty-three months in those with carcinomas of the lower lip unsuccessfully treated.

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## CARCINOMA OF THE MOBILE PORTION OF THE TONGUE

### Anatomy

The tongue is a very muscular organ which lies over the floor of the mouth and has the form of a flattened cone extending anteroposteriorly. The mobile portion of the tongue, its anterior two-thirds, is the portion of this organ which extends anteriorly to the lingual V formed by the vallate papillae. It is this portion of the tongue which belongs in the oral cavity proper. The base of the tongue, situated behind the lingual V, is anatomically situated in the oropharynx.

The superior surface of the tongue is slightly convex, its inferior surface is attached to the floor of the mouth except for its anterior third. The lateral borders of the tongue are rounded and correspond to the dental arches.



Fig 180—An Estlander operation for malignant tumor of the upper lip. The defect of the excision has been filled by a triangular flap from the lower lip



Fig 180

Fig 181

Fig 180—Basal cell carcinoma arising from the skin of the upper lip

Fig 181—Same patient following roentgentherapy



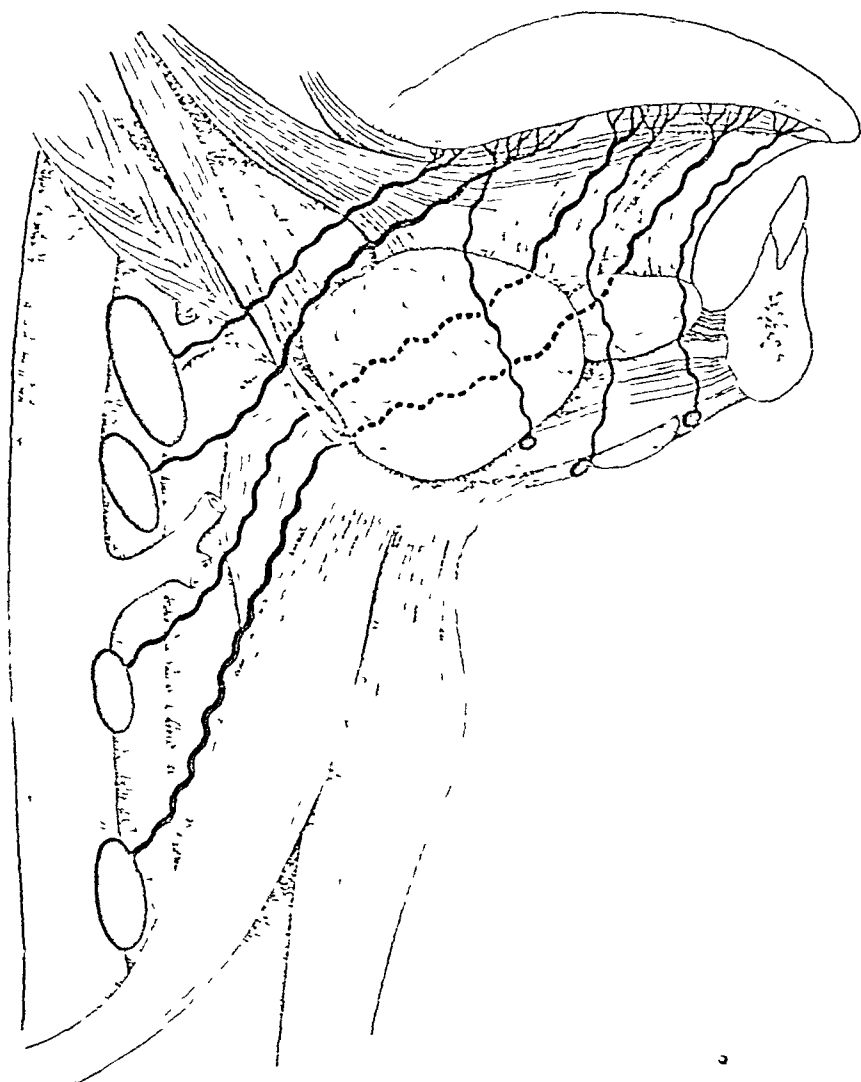


Fig 182—Anatomic sketch of the lymphatics of the tongue illustrating that the farther forward the lateral areas of the tongue are the lower max be their draining lymph nodes

The muscles of the tongue have their strongest attachment on the hyoid bone. They are divided in the midline by a fibrous septum. The tongue is covered by a stratified squamous epithelium beneath which there are abundant mucous and serous glands. The irregular appearance of the dorsal surface of the tongue is due to the presence of numerous and varied papillae. The mucous membrane is firmly adherent to the underlying muscle.

**Lymphatics**—The network of lymphatics of the anterior two thirds of the mobile portion of the tongue is almost entirely independent from that of the base or pharyngeal aspect of the tongue. The network of lymphatics of the mucous membrane is rich and intercommunicates with the equally rich muscular network. These lymphatics gather into several collecting trunks.

*Apical Lymphatics*—The lymphatics of the tip of the tongue gather into two main collecting trunks which run along the direction of the frenulum on each side of the midline. They take a posterior and downward direction pass under the digastric muscle and inside the hyoid bone, and terminate in the supraomohyoid node of the internal jugular chain in the midcervical region. There is a second collecting trunk of lymphatics of the tip of the tongue which ends in the submental nodes, but this is seldom observed in the adult and consequently has no significance in cancer of the tongue.

*Marginal Lymphatics*—These collecting trunks of the lateral border and inferior surface of the tongue may follow two directions. (a) Passing medially to the submaxillary gland they continue toward the nodes on the anterior jugular chain, ending in a node which is situated lower in the neck the more anterior their origin in the tongue (Fig 182). Consequently those lymphatics which drain an area of the lateral border of the tongue near the lingual end end in the subdigastric group of anterior jugular nodes while those closer to the tip of the tongue end near or in the supraomohyoid node previously mentioned. (b) Passing laterally to the submaxillary gland a less numerous group of lymphatics ends in the submaxillary group of nodes.

*Central Lymphatics*—The central lymphatics drain the medial two thirds of the dorsal surface of the tongue covering all the territory anterior to the vallate papillae. These collecting trunks may pass medially to the submaxillary gland and end in the jugular chain of nodes or may follow a course lateral to the submaxillary gland and end in the submaxillary nodes (Fig 183). These trunks often cross the midline to end in the submaxillary and jugular nodes of the opposite side of the neck.

### Incidence and Etiology

Cancer of the tongue is predominantly found in men between 40 and 60 years of age. It is however occasionally observed in younger individuals. The incidence in women is very variable. As an average women do not account for more than one fifth or at the most one fourth of all cases. A greater incidence has been reported in certain countries such as in Sweden where more than 40 per cent of all carcinomas of the oral cavity are found in women. This disproportionate incidence however is explained on the basis of a pre

half were carcinomas of the tongue (Khanolkar). The great majority of them, however, developed on the base of the tongue or glossopharyngeal sulcus and consequently should be considered as oropharyngeal tumors. This high incidence of carcinoma of the oral cavity and oropharynx in India has been attributed to the habit of betel nut chewing, but Khanolkar refutes this argument by pointing out that the incidence is fairly equal in both betel nut addicts and nonchewers. It is true, nevertheless, that betel nut chewing may lead to a bad oral hygiene which often accompanies carcinomas of the oral cavity.

About one-half of all carcinomas of the tongue (46 per cent according to Martin) have some degree of coexisting leucoplakia, and in a great number of instances the lesion has been known to develop from a pre-existent patch of leucoplakia. On the other hand, not all leucoplakias of the tongue or other regions of the oral cavity degenerate into carcinoma. Leucoplakia may persist unchanged for years or disappear with improvement of oral hygiene.

### Pathology

**Gross Pathology**—Carcinomas of the mobile portion of the tongue arise most frequently on the lateral border (Fig. 184). A small proportion arise on the tip of the tongue or its ventral surface, and rarely they arise from a pre-existing area of leucoplakia on the dorsal aspect. In general, there is diffuse induration around and beneath the leucoplakia without any evident ulceration but showing deep crevices. In a study of over 1,000 cases of carcinoma of the oral cavity, Sarasin reported thirty cases in which new separate carcinomas had occurred in the oral cavity. In twenty of these there had been a persistent leucoplakia. When carcinoma arises from leucoplakia, it is often multicentric.

Some lesions of the tongue are predominantly infiltrating and may show extensive involvement without much ulceration. Others present wide and superficial ulceration with some but not very deep infiltration. Still others may present wide ulceration with extensive infiltration of the underlying muscle.

Lesions which develop on the lateral border of the tongue usually extend submucously toward the anterior pillar of the soft palate which they may secondarily invade and ulcerate. They also may extend toward the floor of the mouth but may not reach it until the tumor is far advanced. Lesions of the ventral surface of the tongue directly extend toward the floor of the mouth, and in many instances it is difficult or impossible to establish whether the lesion arose on the tongue or on the floor of the mouth. The ulceration is usually in the form of an elongated, fissurelike loss of substance with submucous and muscular infiltration which rapidly becomes attached to the mandible. As a general rule, the attachment to the mandible does not imply invasion of the bone which is safeguarded by its periosteum. Lesions which develop on the tip of the tongue are usually ulcerating with little infiltration, but cases of extensive involvement and even spontaneous amputation have been reported. Deeply infiltrating carcinomas of the tongue which spread toward its posterior third may invade and perforate the large lingual vessels.

**METASTATIC SPREAD**—The majority of patients with carcinoma of the tongue present metastatic nodes sometime during the course of the disease.

existing Plummer Vinson syndrome a true precancerous condition found among the underprivileged women in that country (Ahlbom)

There is a high incidence of syphilis among men with carcinoma of the tongue (20 to 40 per cent). With the exception of carcinoma of the cervix, where the same association has been noted although in a lesser degree, the coexistence of syphilis and carcinoma of the tongue is unique. In a study of 3,000 cases of cancer in males Levin reported a five times greater incidence of syphilis associated with carcinoma of the tongue than with any other form of cancer. Although these findings suggest that syphilis is one of the causes of cancer of the tongue the coexistence of these factors is not necessarily indicative of a relationship of cause to effect. It has also been suggested that antisiphilitic treatment (arsenic) which is given to most of these patients may also be merited.

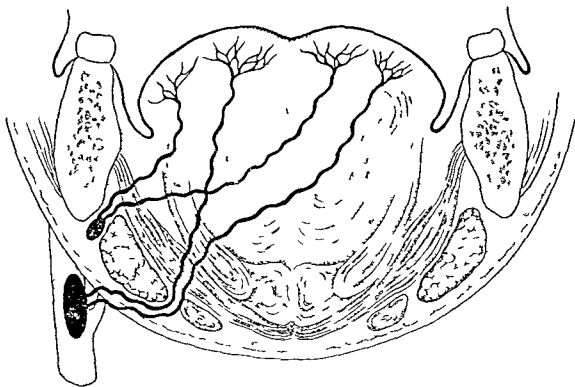


Fig. 183—Anatomic sketch of the lymphatics of the tongue in a frontal section illustrating that the areas of the dorsum are drained by trunks which may cross the midline to enter in subaxillary or cervical lymph nodes of the opposite side (After Rouvière)

Poor oral hygiene is often associated with carcinoma of the tongue for it is not unusual to find a carcinoma of the lateral border of the tongue next to an injuring carious tooth. As in other forms of cancer of the upper air passages the use of alcohol and tobacco has been considered one of the coadjutant factors in the production of carcinoma of the tongue. An electric current induced between two dental fillings of different metal compounds has also been suspected as a contributing factor (Rovner and Cantril).

In India there seems to be a predominance of carcinomas of the oral cavity and oropharynx over other forms of cancer. Of 2,880 cases of cancer observed at the Tata Memorial Hospital of Bombay between 1941 and 1943 there were 1,000 cases of carcinoma of the oral cavity and oropharynx of which over one

usually with considerable inflammation. If the tumor burrows farther into the tongue, it is not infrequent, particularly in the undifferentiated varieties, to see tumor cells lying within the lumen of lymphatics. The muscle is destroyed by the invading tumor. In spite of the high association of syphilis, it is infrequent that definite microscopic evidence of syphilis is present. The presence of plasma cells and fibrosis is not enough to make such a diagnosis, and other subsidiary findings such as vascular changes and gummatous lesions are infrequently observed.

### Clinical Evolution

The most common presenting symptom of carcinoma of the tongue is a growth or very slight local pain. Usually there is coexistent poor oral hygiene, and not infrequently the growth is lying against a carious tooth. Later, when the tumor becomes ulcerated and secondarily infected, *otalgia* on the same side as the lesion, a certain degree of *hypersalivation*, and *dysphagia* may occur. Except perhaps in the very early stages of the disease, *pain* is a very important symptom. In a great number of cases, it may become excruciating and radiate to the entire side of the face and head.

In the beginning, the primary lesion appears in the form of a slightly raised, indurated but nonulcerated area, presenting only deep-bleeding crevices. As the area of induration extends, the center of the tumor then becomes ulcerated and secondarily infected. There is, at times, accompanying glossitis or stomatitis. With infiltrating lesions the movements of the tongue become more and more limited.

*Adenopathy*.—About 40 per cent of all patients with carcinoma of the tongue are first examined after a metastatic adenopathy has already developed, and about 40 per cent of those without nodes when first seen develop an adenopathy later. Although a metastatic adenopathy may develop early in the evolution of the disease, the chances of its appearance become greater the longer the tumor has been present, and these chances are also greater as the primary lesion increases in size. Taylor and Nathanson reported that of the patients whose primary lesion had been present for three months, 40 per cent presented a coexisting metastasis, and that 90 per cent of those whose lesions had been present for a year had already developed metastases. They also found that only 22 per cent of the primary lesions measuring 1 cm in diameter presented a metastatic node, while 92 per cent of those measuring 4 cm were accompanied by a metastasis.

Metastatic nodes from a primary lesion of the tongue are most commonly found in the upper cervical region just below the angle of the mandible at the level of the carotid bulb area. Less frequently, nodes will be found in the submaxillary region or lower in the neck. Involved submental nodes are rare. Individual nodes rarely grow to large dimensions. The progress of this metastasis is rather toward the production of new metastatic implants. Bilateral metastases are not infrequent, particularly in the more advanced group of cases and in the lesions which develop in the midline. In 306 cases of carcinoma of the anterior two-thirds of the tongue in which the lesion was strictly unilateral, Roux-Berger found only 6 per cent of bilateral metastases,

This was true of 586 (71 per cent) of 822 cases studied by Taylor and Nathanson. The most frequently invaded nodes are those in the subdiaphragmatic group. A metastatic adenopathy is commonly found on the anterior jugular chain and is lower in the chain the closer the lesion is to the tip of the tongue. Submaxillary nodes are also involved but with lesser frequency. A thorough pathologic study, however, will reveal evidence of metastases in nodes barely visible to the naked eye. Bilateral metastases are not uncommon but they are considerably more frequent in cases where the lesion approaches or crosses the midline.

Carcinomatous nodes from a primary lesion of the tongue have a tendency to multiply in number rather than to increase in volume. They are often attached to the deep structures of the neck and the mandible. A high degree of secondary infection often accompanies these metastatic nodes. Purely inflammatory nodes are also found.



FIGURE 1. A. Ductal carcinoma of the tongue. B. Metastatic carcinoma of the tongue.

Ductal metastases from carcinoma of the tongue are usually only visible in the early stages of the disease but they are often found in cross-sections of the lymph nodes prepared with the technique of Mallory.

**Microscopic Pathology.** The characteristic histological features of the metastatic carcinoma of the tongue are those of the primary carcinoma. The metastatic carcinoma is usually of the ductal type. A few of the metastatic carcinomas are of the squamous type.

When a metastatic carcinoma is found in a lymph node, it is usually found in the form of a small, dark, irregular mass. The mass is usually surrounded by a thin layer of connective tissue. The mass is usually composed of a few cells, which are usually arranged in a ductal pattern. The cells are usually large and have a high nuclear to cytoplasmic ratio. The nuclei are usually hyperchromatic and the cytoplasm is usually scanty. The cells are usually arranged in a ductal pattern, which is characteristic of ductal carcinoma.

only with one hand, and there may be some advantage in palpating the neck while standing behind the seated patient

Frequently, because the primary lesion is secondarily infected, enlarged nodes may be merely inflammatory, and it is impossible to decide clinically whether they are metastatic or not. The chance of their being metastatic,



Fig. 185—Cavernous hemangioma of the tip of the tongue



Fig. 186—Multiple hemangiomas of the oral cavity in a young woman showing characteristic shiny appearance

however, increases with their size. Taylor and Nathanson found that only 20 per cent of the nodes under 1 cm. in diameter were shown to be metastatic, while 99 per cent of those reaching a diameter of 3 cm. showed evidence of carcinomatous involvement.

while in 188 cases where the lesion was close or beyond the midline, he found 32 per cent of bilateral metastases. On the opposite side of the neck the metastases are more often found in the submaxillary and upper cervical region. Seldom are supraclavicular nodes involved by disease.

Left to themselves, patients with carcinoma of the tongue usually die within a short period of time because of hemorrhage, aspiration pneumonia, or some other complication. In addition when intense pain is present, the administration of sedatives and hypnotics contributes to the further deterioration of the general condition. Distant metastases from primary carcinoma of the tongue used to be considered a rather rare occurrence, but with the improved results in the treatment of the primary lesion and the regional lymph node metastases, a greater percentage of distant metastases has been observed recently (Lenz, Sachs, Braund).

### Diagnosis

When a carcinoma of the tongue is suspected, an effort should always be made to establish the approximate duration of symptoms and of the lesion, for this information may have a bearing on the therapeutic decisions. The intensity of any pain should also be recorded because it may give a clinical idea of the differentiation of the tumor and its infiltrating ability.

It should be remembered that early diagnosis of carcinoma of the tongue is often missed not because the patient delays consultation, but because of the apparent innocence of very early lesions. The dentist in particular, is in the unique position of observing these early lesions and of obtaining the pertinent clinical history. He also has the unparalleled opportunity of observing areas of leucoplakia and of following their development. Consequently, his diagnostic and therapeutic knowledge are of utmost importance (Burford, Buschke). A greater instruction and training in the early diagnosis of oral tumors is for this reason, desirable in the dental schools.

Areas of leucoplakia of the oral cavity should be observed closely and frequently, and biopsy should be done at the earliest sign of ulceration or thickening.

**Clinical Examination**—The examination of the tongue should never be limited to the description of the visual findings. There should be a thorough palpation of the tumor area, for this often results in doubling the visual appreciation of the actual volume of the tumor.

The palpation of the neck in search for metastatic nodes should be thorough. An inflammatory enlargement of the submaxillary gland may often be confused with a metastatic node, but the inflammatory enlargement of the submaxillary gland is usually discoid in shape and there is no neoplastic induration. Bimanual palpation of the submaxillary region with a finger placed in the floor of the mouth may help to eliminate errors. The cervical region proper should also be investigated, particularly at the level of the carotid bulb. When both sides of the neck are palpated at the same time the examiner may unconsciously push the hyoid bone toward one side and have the impression of palpating a node with the other hand. This may be obviated by palpating



**ROENTGENTHERAPY**—External irradiation of carcinoma of the tongue through the cheeks and through the submaxillary regions results in considerable diminution of the secondary infection and inflammation as well as in subjective improvement. Alone, however, it rarely succeeds in sterilizing carcinoma of the tongue. Even after the superficial ulcerations are healed, the tumors recur within the substance of the muscles. But external irradiation can be used to great advantage as a preliminary step to interstitial curietherapy. When it is used in this way, the daily dose and the total dose have to be kept at a low level so that the subsequent interstitial irradiation may be given without danger of necrosis. In advanced cases, external irradiation considerably reduces the palpable area of the tumor, facilitating the completion of this treatment by implantation of radium needles to a smaller area. Richards reported improvement in his results by administering external roentgentherapy as a preliminary step to interstitial curietherapy.

**Peroral Roentgentherapy**—The administration of roentgen rays through the opening of the mouth is seldom satisfactory because it is often impossible to cover the entire tumor area in the field which is limited to the opening of the mouth and because it cannot be adequately directed toward the floor of the mouth. This procedure is indicated only for very limited areas without marked infiltration, or in those limited to the anterior third of the tongue.

**INTERSTITIAL CURIETHERAPY**—Interstitial curietherapy has proved to be the most effective form of treatment in the majority of cases of carcinoma of the tongue. Its ability to eradicate rather advanced lesions remains a definite asset over even the widest surgical excisions. Carcinoma of the tongue is one of the few remaining, if not the last, lesion for which this form of treatment is indicated.

Interstitial curietherapy, or radium-puncture, consists of the introduction of sources of radiations into the substance of the tumor. Its correct execution implies that the neoplasm be readily accessible in order that the distribution of the radiating sources be as homogeneous as possible. The best results seem to have been obtained by the use of low-content radium element needles made of platinum, usually 15 to 30 mm. in length. The radiations are filtered through a thickness of 0.5 cm. of platinum which eliminates the least desirable, low quality form of radiations. The needles are inserted parallel to each other, about 1 cm. apart. It may be desirable for the direction of the needles to be changed to a perpendicular plane after half of the total dosage has been given (Fig. 187). Holding these needles in place requires continuous attention and is rather uncomfortable for the patient, but it is preferable to use needles of low radium content and to protract the treatment over a period of eight to ten days. This procedure requires great skill on the part of the radiotherapist, because the margin between an insufficient dose and one which will produce radionecrosis is very narrow. It requires a careful evaluation of the volume of the tumor and the administration of a corresponding dose. Because most of these lesions present extensive secondary infection and because of concomitant radiation reactions or dysphagia, a few patients may develop an

**Biopsy**—Biopsy specimens from an ulcerated lesion of the tongue should be taken with a scalpel, for specimens which are taken with a grasping or even a cutting forceps are usually insufficient and limited to the more superficial layers of the lesion. A wedge shaped specimen, including some of the surrounding normal mucous membrane, should be taken from the borders of the ulceration. One or two sutures may be necessary to avoid excessive bleeding.

In the majority of instances, an aspiration biopsy of the nodes has only an academic interest inasmuch as, if the results are negative, the possibility of a metastasis somewhere in the neck is not necessarily eliminated, and consequently, it does not preclude the indication for a radical neck dissection. However, when the metastatic nodes are to be treated with radiation therapy, a previous positive aspiration biopsy is the only proof that radiation therapy, in itself, was the means of cure.

**Differential Diagnosis**—Areas of pure leucoplakia of the tongue which have been injured or infected might offer a difficulty in diagnosis and can be clarified only by a competent microscopic examination of biopsy specimens. Tuberculous lesions of the tongue are usually painful circumscribed and nonindurated ulcerations without deep infiltration of the muscle. They are secondary to pulmonary tuberculosis. A primary syphilitic chancre, usually found toward the tip of the tongue may sometimes give the impression of an early carcinoma. Differential diagnosis should be done both by dark field examination of the exudate and by biopsy in view of the possibility of the coexistence of the two conditions.

Inflammatory conditions of the tongue are easily eliminated on the basis of their rapid development, extensive areas of tenderness, and lack of definite ulceration or induration. Localized areas of inflammation caused by injury, particularly on the lateral borders, might be more difficult to differentiate and may require a microscopic examination. Liechmann called attention to the frequent error in diagnosis connected with the development of a lingual tonsillitis. This consists of a hypertrophy of the organ folliculum situated on the tongue at the insertion of the anterior pillar of the soft palate.

### Treatment

Although there is wide agreement on certain phases of the treatment of carcinoma of the tongue and its cervical metastases there is still some diversity of opinion about the methods of approach and the techniques to be used.

#### Treatment of the Primary Lesion —

**SURGERY**—A surgical excision of a carcinoma of the tongue is not always successful; it requires that the lesion be small and the excision wide. This eliminates surgical treatment in a large number of cases which show local extension. The excision of a small primary lesion may be justified in some instances, however, as a matter of expedience in order not to delay the surgical excision of metastatic nodes already present. Time will thereby be gained at the expense of mutilation and loss of function of the tongue.

**ROENTGEN THERAPY**—External irradiation of carcinoma of the tongue through the cheeks and through the submaxillary regions results in considerable diminution of the secondary infection and inflammation as well as in subjective improvement. Alone, however, it rarely succeeds in sterilizing carcinoma of the tongue. Even after the superficial ulcerations are healed, the tumors recur within the substance of the muscles. But external irradiation can be used to great advantage as a preliminary step to interstitial curie therapy. When it is used in this way, the daily dose and the total dose have to be kept at a low level so that the subsequent interstitial irradiation may be given without danger of necrosis. In advanced cases, external irradiation considerably reduces the palpable area of the tumor, facilitating the completion of this treatment by implantation of radium needles to a smaller area. Richards reported improvement in his results by administering external roentgen therapy as a preliminary step to interstitial curietherapy.

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aspiration bronchopneumonia which may be confused with pulmonary metastases (see Carcinoma of the Hypopharynx, page 387)

Interstitial irradiation by means of radium emanation seeds has been advocated and has been made available to practitioners everywhere. However, the placement of the sources of radiations throughout the entire tumor area is very difficult and consequently the chances of a local recurrence are high, also postirradiation necrosis is more frequent because of the weak filtration of these minute sources of radiations

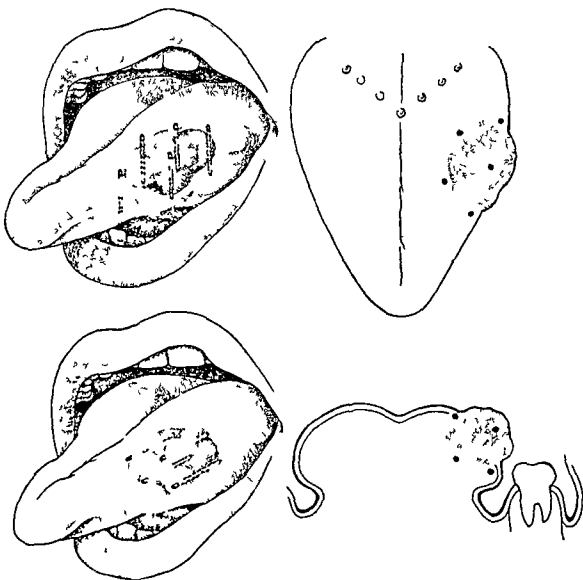


Fig. 15.—Technique of interstitial irradiation of carcinoma of the tongue by means of radium element needles. The needles are first implanted as above and after half of the dosage has been given they are placed as illustrated below in a perpendicular direction. Thus a homogeneous irradiation is assured.

**Treatment of the Cervical Adenopathy**—A rather large proportion of patients with carcinoma of the tongue develop an adenopathy. The final results obtained for the entire group of carcinomas of the tongue depend, in great part, on the results of the treatment of metastatic cervical nodes.



FIG. 188—Carcinomas of the tongue before and after radiotherapy. Treatment consisted of external roentgentherapy followed by interstitial curietherapy (Courtesy of Toronto Institute of Radiotherapy Toronto General Hospital Toronto Can)

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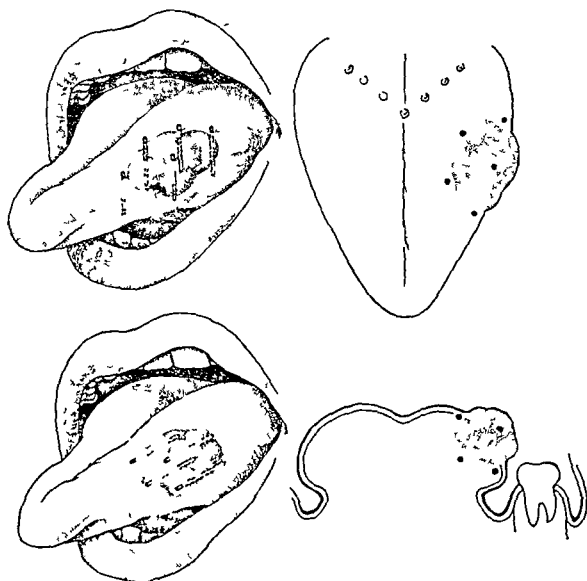


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**SURGERY**—The accepted treatment of a metastatic cervical adenopathy from a primary carcinoma of the tongue is a *radical neck dissection*. There can be no compromise in this choice. Local excisions of nodes or even partial neck dissections should not be done, they are worse than abstention.

A radical dissection implies the block excision of the submaxillary contents, the sternocleidomastoid muscle, and the internal jugular vein, and the nodes, fat, and connective tissue which surround these structures, from the midline to the anterior border of the trapezius muscle and from the mandible to the clavicle. This classical operation, the technique of which was perfected by Martland and Crile, is sometimes handicapped by the fact that the most commonly invaded nodes (the subdigastric group) are very close or partially hidden below the upper limit of the dissection. The resection of part of the angle of the mandible has been suggested but is of little worth. Roux-Berger suggested the extension of the operation by dividing the posterior belly of the digastric muscle at its insertion on the hyoid bone. This appears to be the most useful means of gaining several centimeters and to perform a higher ligation of the internal jugular vein, after the subdigastric group of nodes has been largely exposed (Fig. 189).

Duffy outlined the following conditions as prerequisites for a therapeutic neck dissection:

- 1 The primary lesion should be controlled
- 2 The primary lesion should be limited to one side of the mouth
- 3 The carcinoma should show marked histologic differentiation
- 4 The metastases must be limited to one group of nodes in two contiguous cervical triangles
- 5 The capsule of the nodes must not have been perforated by carcinoma
- 6 There must not be an adenopathy on the opposite side
- 7 There must not be a distant metastasis present
- 8 The patient should be in good general condition

Without denying the good sense of the preceding criteria, it might be well to emphasize that they restrict considerably the indications for a neck dissection and that a more liberal choice of cases is often justified.

**Control of Primary Lesion**—A neck dissection is not justified before the primary lesion has been treated and healed, mainly because of the frequent infectious complications which result from such a procedure. The certainty of the control of the primary lesion, however, is a matter of time, and no more time should be lost than is justifiable. All that can be asked is that the primary lesion be treated and that it be healed before the neck dissection is done.

**Extension of Primary Lesion**—That the primary lesion of the tongue may not be strictly limited to one side only increases the chances of bilateral metastases, but this is not a real contraindication to the operation. Tailhefer concluded that a prophylactic neck dissection on the opposite side should also be done whenever the primary lesion approaches or goes beyond the midline.

**Degree of Differentiation of the Tumor**—The histologic character of the primary lesion is, of course, important, but only in the rare cases of a highly

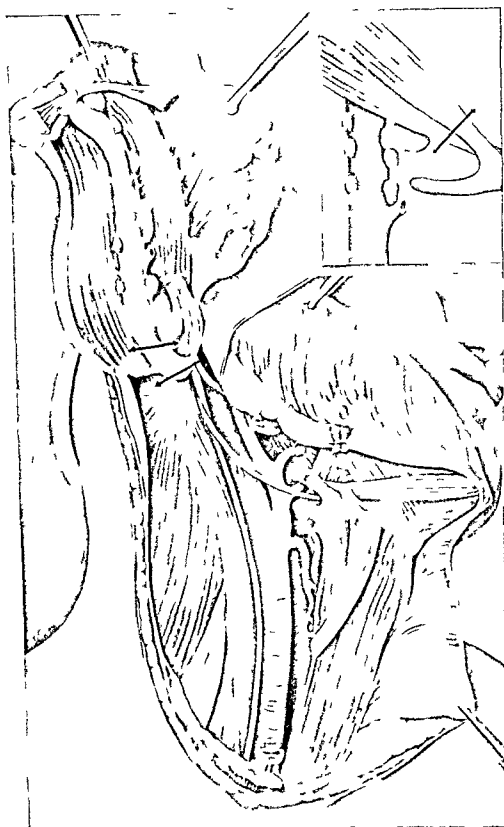


Fig. 12.—Radical neck dissection. Division of the Sternocleidomastoid muscle near its lower insertion facilitates radical removal of nodes (Courtesy of Dr. Louis Berger, Director, The Radium Institute, University of Paris.)



involvement of the nodes. It should be said here that the percentage of such reported involvement greatly depends on the thoroughness of the pathologic examination.

A radical dissection may result in partial facial paralysis, paralysis of the trapezius, with a corresponding drop of the shoulder, often accompanied by pain. At times there are also sensory troubles such as hyperesthesias of the neck and shoulder. These shortcomings should be presented to the patient before the operation so that he may accept them more readily if they follow.

**RADIOTHERAPY**—For treating metastatic lymph nodes from a carcinoma of the tongue, radiotherapy is justified only as a form of palliation after a radical dissection has been ruled out. There is no doubt that external irradiation can sterilize a carcinomatous lymph node, but in carcinoma of the tongue even when there appears to be only a single metastatic node in the submaxillary or upper cervical region, the attempt to sterilize it is futile because of the certainty that multiple other microscopically invaded nodes are present. A thorough examination of the surgical specimens provides the strongest argument against such a method of approach.

External roentgentherapy may be applied usefully to metastatic cervical lymph nodes while the primary lesion is healing. The daily and total dose do not need to be very high, and the limits of important skin reactions should not be reached. The purpose, of course, is to retard the development of the metastases and to diminish inflammation but not to eliminate the important and definite indication of a neck dissection. In a few instances, just for academic interest, we have delivered a large dose of external irradiation to a metastatic lymph node (proved by aspiration biopsy) during this waiting period. Examination of the surgical specimen after neck dissection showed no evidence of carcinoma in the irradiated node, but carcinoma was present in several other nodes of the neck where it had not been clinically suspected.

**Prophylactic Treatment of Cervical Metastases**—The prophylactic treatment of cervical metastases means the administration of treatment before the metastatic lymph nodes have become clinically evident. By this treatment it is hoped that in a sizable number of instances the procedure will be therapeutic for early, undetected metastases in their subclinical stage.

The prophylactic treatment of metastatic neck nodes by administration of small amounts of radiation through large fields is without a reasonable basis. No matter how early the carcinomatous implants, they will not be sterilized unless a minimum total amount of radiation is given. It would not be justified to give this necessary minimum amount of radiations to a field covering the entire neck.

A *prophylactic neck dissection* in patients with carcinoma of the tongue has unquestionable merits. It must be understood, in the discussion of this controversial issue, that arguments which are valid against the prophylactic neck dissection in carcinoma of the lower lip do not apply when carcinoma of the tongue is considered. The issue is only confused by talking of prophylactic neck dissections in relation to carcinoma of the oral cavity in general.

undifferentiated tumor is a neck dissection contraindicated. These undifferentiated tumors develop rapid growing metastases which are, most of the time a step ahead of the operative procedure and thus constitute a righteous contraindication to neck dissections.

*Extension of the Adenopathy*—It is fairly typical of carcinomas of the tongue to metastasize to nodes at different levels of the neck almost simultaneously. The pathologic study of surgical material will reveal that microscopic invasion of midcervical nodes is not infrequent when upper cervical or submaxillary lymph nodes are also invaded. The presence of metastatic nodes in two contiguous cervical triangles is thus the rule rather than the exception. When these nodes become moderately enlarged however, in either triangle they are usually adherent to surrounding structures or to the skin and it is rather on this basis that the probable benefit of the neck dissection should be evaluated.

*Invasion of the Capsule of the Lymph Node*—It is clinically assumed that the capsule of a lymph node has been invaded when the node has become adherent to the mandible, the muscles, or to the skin. Such invasion of adjacent structures restricts considerably the possibilities of controlling the disease by neck dissection, but not invariably so. Although the prognosis of a carcinoma adherent to the mandible is not as favorable as that of metastatic carcinoma from the lower lip (Sugarbaker) it may be justified in certain instances to perform a neck dissection and to accompany it by excisions of fragments of the skin or the entire horizontal branch of the mandible. The operative mortality is greater, but these enlarged operations offer the only chance of cure.

*Bilateral Metastases*—A clinically evident metastasis on the opposite side of the neck obviously darkens the prognosis but bilateral neck dissections have been performed successfully in such cases. The problem here is that of resecting both internal jugular veins and handling the unquestionable disturbances which result in some instances but consecutive ligation of both internal jugulars is possible and may be warranted in certain instances (Tulhefer Fischel). Leclerc made a study of this problem and insisted on the advisability of starting by a neck dissection on the side opposite the lesion. The purpose of this procedure is to save the opposite internal jugular when possible and to resect it only if necessary profiting by the fact that the tumor may have already progressively compressed the internal jugular vein on the side of the lesion. An interval of a few weeks may be necessary between the two operations.

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A neck dissection is, of course equally indicated if metastatic nodes develop after the primary lesion is treated. In these cases, it always must be made certain that the primary lesion remains controlled. Nodes that become enlarged may or may not be metastatic and in so far as an aspiration is not conclusive, a neck dissection is always indicated. Roux-Berger performed ninety-four neck dissections on patients with carcinoma of the tongue and enlarged cervical lymph nodes and only sixty-one showed definite microscopic

TABLE VII. RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS  
 CARCINOMAS OF MOUTH FOLLICULOSIS OF TONGUE—NICK DISSECTION, 1919-1931,  
 (Data from Roux Bauger and Tullie Bull Assoc Iring p 1 etude du cancer, 1939)

CASES	TOTAL NUMBER	HISTO- LOGIC AL FINDINGS	LOCAL EXTENSION	LOCAL EXTENSION OF TUMOR	DISTANT METASTASES	PHASE OF DISSECTION	CAUSE KNOWN	WITH INFILTRATION	OF WHICH WITH POSITIVE NODES	PERCENT AGE OF GROUP HAVING FIVE OR MORE
1	70	--	20	5	0	10	1	25	--	31
2	60	31	26	1	1	1	1	23	9	38
3	91	33	29	21	11	11	3	25	10	27
4	34	61	11	7	2	6	0	6	6	18
A	91	91	--	--	--	--	--	16	16	17
B	60	0	--	--	--	--	--	29	0	50

\*Tumors of these patients received postoperative irradiation (radium molds--telecurietherapy) with not as good results as in the group treated surgically only.

Thirty-four of these patients received postoperative irradiation. No improved results.

\*Two of these coincided with a local recurrence.

\*Not all cases which developed nodes came back or were operable when seen.

\*Twelve of these cases had postoperative curietherapy with no appreciable improvement of results.

The relative merits of a prophylactic neck dissection may be best judged on the basis of the following factors (Regato)

- 1 The percentage of cases which, not having metastases at the time of treatment of the primary lesion, will develop one later
- 2 The chances of a permanent local sterilization of the primary lesion after adequate treatment
- 3 The comparison of the cure rate of prophylactic neck dissections (in which the nodes are found histologically positive) and the cure rate of therapeutic neck dissections (done on equally positive nodes which have become palpable)
- 4 The number of patients lost through inoperability because the operation is deferred
- 5 The operative mortality of neck dissections

1 Whether they present a palpable node or not when first seen, the *majority of patients with carcinoma of the tongue will develop a metastasis*. In a series of 320 patients who did not have metastases at the time of admission to the Memorial Hospital of New York 129 (40 per cent) subsequently developed metastatic lymph nodes. This is indeed a high percentage of cases and is in itself an indication for prophylactic dissection. It may be added that most of these metastases occur within the six months following the treatment of the primary lesion. It is also true that a good number of these neck node metastases are accompanied or preceded by a recurrence of the primary lesion. Roux Berget reported on 108 patients with cervical lymph node metastasis seventy nine of whom had a coexistent local recurrence. Authors who stand against the practice of prophylactic neck dissections give great emphasis to this argument in the controversy. Martin stated that in a series of 118 of his patients (1927-1934) with primary carcinoma of the tongue and without an adenopathy at the time of admission, only 22 per cent developed a cervical adenopathy *without a recurrence of the primary lesion*. He concluded that if a prophylactic neck dissection had been done in all of them, the operation would have been useless in 78 per cent. By an unexplained restriction of his choice of cases to a smaller group (1931-1934), Martin later reduced from 22 to 12 per cent his own estimate of the percentage of patients who would have profited by the operation. It would seem logical to seek the advantage of a larger rather than of a smaller group of cases.

It must be admitted that a number of prophylactic neck dissections may be rendered useless because of uncontrollable recurrence of the primary lesion. This only means however that the prophylactic neck dissection might have been useless to those with recurrence but does not deny its usefulness to the others. Unfortunately cancer therapy abounds in examples of this nature in which a large amount of work painfuling procedures, and observations are nevertheless justified by whatever small results are obtained.

2 *The chances of a permanent sterilization of the primary tumor are rather high, regardless of extension, provided adequate treatment is given.* The results of course vary according to the different techniques and institutions

### Prognosis

*Clinical Classification*—Different authors have made worthy attempts to classify carcinomas of the tongue in different stages in order to provide a basis for prognosis. It would be relatively easy to classify the primary tumor according to dimensions. In reality, however, the turning point in the prognosis of carcinomas of the tongue is the actual production of a metastasis, regardless of the dimensions of the primary lesion. Richards has proposed a classification of the primary lesion in four stages and of the secondary involvement in three stages. The difficulty still resides in the correlation of these two stagings. A large primary lesion without metastases has a better prognosis than a smaller one which has already metastasized.

Adequate treatment will succeed in healing a large percentage of primary carcinomas of the tongue. Of 191 patients treated at the Radium Institute of Paris, 272 (56 per cent) were without recurrence during the subsequent course, but only 118 (23 per cent) were well and free of disease at the end of five years. Of 556 patients treated at the Memorial Hospital of New York, the disease appeared controlled in 124 (22 per cent) after five years. The wide difference between the ability to control the primary lesion and the final five-year cure rate is, of course, explained by the relatively poor results in controlling the secondary adenopathy.

The prognosis of patients presenting an operable adenopathy at the time of treatment of the primary lesion varies according to the different authors. On an undisclosed number of such patients operated on by Martin, the final five-year cure rate was 8 per cent. In a series of sixty-one neck dissections with pathologically verified metastases Roux-Berger reported a higher cure rate with 16 per cent of the patients living and well at the end of five years. The cases without metastatic adenopathy when first seen, as a rule have smaller lesions of shorter duration and so the chances of permanent control are probably slightly more favorable than average. Those which never develop a metastasis are only subject to failure due to local recurrences, and then life expectancy should closely parallel the percentage of local sterilizations. Of sixty patients operated on by Roux-Berger (prophylactically and therapeutically) who showed no pathologic involvement of the nodes twenty-nine (50 per cent) were living and well at the end of five years. Those which subsequently develop nodes represent a variable group. Many among them will not be operated on. Those patients who benefit from a neck dissection have a five-year cure rate of about 18 per cent (Roux-Berger and Martin). If an early prophylactic neck dissection is systematically done in all patients without clinical evidence of metastasis, there will be a higher percentage of five-year cures (about 27 per cent according to Roux-Berger) than in the group with clinically evident metastasis.

It is clear that the important point in the prognosis of carcinomas of the tongue is the presence or absence of actual node involvement and the early or delayed treatment of such metastasis. For this reason, lesions which have been present for a short time or which have not become very large have a fair prognosis, but the metastasizing ability of the tumor partly reflected in its

and have an important bearing on the question. The best results yet reported, those of the Radium Institute of the University of Paris, showed that 56 per cent of patients did not have a local recurrence at any time after treatment of the primary lesion.

3 Considering only the patients with pathologically proved metastases, *the five year cure rate is greater for the group treated prophylactically*. Roux Berger performed ninety four therapeutic neck dissections in which the nodes were found invaded, with a five year cure rate of 17 per cent (sixteen patients well five years). He also performed sixty prophylactic neck dissections and found that more than one half (thirty three) had microscopic evidence of metastases. The five year cure rate for these thirty three was 27 per cent (nine patients well five years). The far from negligible difference is in favor of the prophylactically treated group (Table VII).

4 In spite of a good follow up, *a number of patients will be lost through inoperability* when the operation is not done prophylactically and thus will never have the benefit of a therapeutic neck dissection. The incidence of these cases is a variable one but some will be found in all clinics. These failures are due to rapid increase in the rate of growth of metastatic nodes and invasion of the adjacent structures.

5 With recent advances in the knowledge of shock and the treatment of infections, *the operative mortality has been reduced to very reasonable limits*. The operative mortality following neck dissections used to be between 10 and 12 per cent when general anesthesia was used. This figure rapidly dropped as soon as regional anesthesia was introduced. Martin's mortality rate on 210 neck dissections was 2.4 per cent, and Roux Berger had a 2.5 per cent mortality rate on 200 neck dissections. In addition it may be stated that the duration of the procedure, the incidence of secondary infection and consequently the general risk are considerably less in prophylactic neck dissections than in the therapeutic.

In conclusion, we believe that a prophylactic neck dissection is justified after the treatment of primary carcinoma of the tongue. While it is impossible to foresee which patients will benefit by the procedure it is unquestionable that a number of them will for the following reasons: (1) because of the great percentage of patients with carcinoma of the tongue who will ultimately develop metastatic nodes, (2) because in a majority of prophylactic dissections the nodes will be found to contain carcinoma, (3) because when the nodes are invaded the chances of a permanent cure are greater than if the operation has been postponed until the nodes became palpable, (4) because not all patients who later develop nodes profit by the operation while they all equally benefit by it if it is done prophylactically, (5) because the operative mortality in the hands of a competent surgeon is so small that the risk to a patient who would not have eventually developed nodes is justified by the greater number of patients saved, (6) because practical considerations of the amount of work done are irrelevant when one is sure of a greater percentage of final cures.

It must be added that in choosing a group of patients in whom a prophylactic neck dissection will be most beneficial, those with the larger sized primary lesions and those whose lesions have been present longer are ideal.

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## CARCINOMA OF THE FLOOR OF THE MOUTH

### Anatomy

The floor of the mouth or inferior wall of the oral cavity is a semilunar area circumscribed anteriorly by the lower dental arch and posteriorly by the inferior surface of the tongue (Fig 190) In depth the floor of the mouth extends to the mylohyoid muscle which separates it from the suprahyoid region It is divided in the midline by a mucous fold, the frenulum, on each side of which a small nodule with a central orifice (the openings of the canal of Wharton) can be seen Lateral to these there are two smaller orifices corresponding to the canals of the sublingual glands

The floor of the mouth is covered by the same squamous epithelium which covers the rest of the oral cavity Below the mucous membrane are found the sublingual glands, the anterior pole of the submaxillary gland with its canal, and numerous vessels and nerves

**Lymphatics**—The lymphatics of the floor of the mouth are continuous with those of the tongue and sublingual gland, they empty into the submaxillary nodes and those of the anterior jugular chain Laterally the lymphatics of the floor of the mouth are continuous with those of the lower alveolar ridge (Rouvière)

### Incidence and Etiology

Ducuing reported an incidence of less than 0.5 per cent of carcinomas of the floor of the mouth in relation to the total number of cancers in his clinic At the Memorial Hospital in New York, cancer of the floor of the mouth represents 17 per cent of all oral malignant tumors The age incidence is very simi

microscopic features should also be taken into consideration. Lesions which develop near the midline or which have invaded beyond it will have a worse prognosis because of their potential ability to metastasize to the opposite side of the neck. Carcinomas invading the anterior pillar of the soft palate or which have actually invaded the mandible have a very bad prognosis because of frequent failure to be locally sterilized. Aged patients seldom stand the necessary treatments and are subject to greater possibilities of complications. The curability of cancer of the tongue in women appears at this time to be less, all other circumstances equal, than in men. This contrasts sharply to the apparent greater curability of carcinoma of the oropharynx and nasopharynx in women.

Postirradiation recurrences in the tongue can benefit by a wide surgical excision. Roux-Berger reported forty excisions of postirradiation recurrences resulting in four (10 per cent) five year survivals.

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Metastatic implants in the anterior jugular chain of lymph nodes also take place, but this seldom occurs until after the tumor has metastasized to the submaxillary region. Most carcinomas of the floor of the mouth develop an adenopathy sometime during the course of the disease. Martin and Sugarbaker found only one instance of distant metastases in twelve cases of carcinoma of the floor of the mouth that came to autopsy.

**Microscopic Pathology**—Most carcinomas of the floor of the mouth are moderately differentiated epidermoid carcinomas.



Fig. 161.—Typical fissure-like carcinoma of the floor of the mouth extending to the anterior midline. (Courtesy of Dr. Simon T. Cantrell, Tumor Institute, Swedish Hospital, Seattle, Wash.)

### Clinical Evolution

The most common presenting symptom of carcinoma of the floor of the mouth is an indurated growth felt by the tip of the tongue. Later, when the tumor becomes ulcerated, there may be *otalgia*, *hypersalivation*, and progressive *difficulties in speech*. *Bleeding* may occur, but hemorrhage is infrequent.

About one-fourth of all the patients present a submaxillary adenopathy when first seen. This is often bilateral and adherent to the mandible. In many instances the submaxillary tumefaction is actually a direct extension of the tumor.

A few carcinomas of the floor of the mouth may be inconspicuous and their clinical onset is characterized by development of a submaxillary aden-

lar to that of carcinoma of the tongue these lesions of the floor of the mouth occur most frequently in patients 50 to 60 years of age

As in other forms of carcinoma of the oral cavity, poor hygiene and tobacco have been considered as causative factors but the proportion of cases which develop from a previous area of leucoplakia is smaller than in carcinoma of the tongue

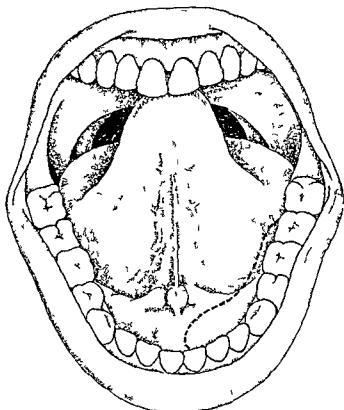


Fig 190 — Anatomical sketch of the floor of the mouth showing projection of the sublingual gland (dotted line)

### Pathology

**Gross Pathology**—Carcinomas of the floor of the mouth arise most often on one or the other side of the midline and in most instances present only a deep fissurelike ulceration, the bulk of the tumor having developed submucosally (Fig 191). In other instances the tumor is superficially ulcerated throughout without apparently invading in depth (Fig 192). These tumors rapidly extend beyond the midline and become adherent to the inner aspect of the mandible, their extension into the tongue is less frequent. However, there are instances in which it is difficult to establish whether the tumor had a lingual origin or whether the tongue was invaded secondarily. Direct extension of the tumor to the submaxillary and sublingual glands is sometimes observed, or it may extend through the muscular layer to the submaxillary region.

**METASTATIC SPREAD**—Metastases are more often found in the submaxillary region than in carcinoma of the tongue and they are also more often bilateral

some instances this produces considerable pain and dysphagia and is accompanied by a hard bilateral tumefaction of the submaxillary regions which may appear as a characteristic adenopathy. In these cases however the absence of ulceration, the relatively rapid progression of the condition and periods of spontaneous improvement militate against the diagnosis of carcinoma. This constellation of the submaxillary and sublingual ducts is most often due to calculus plugs. A tumor is more often unilateral and cystic retention of secretions of the sublingual or submaxillary glands due to salivary calculus. There is no ulceration, the tumor fluctuates and the roentgenogram may show calcified calculi. Sublingual salivary gland tumors are rare (Smith). They are slow growing, no ulcerated and rubbery in consistency and have a typical cystic appearance (see Tumors of the Salivary Glands).

### Treatment

**Treatment of the Primary Lesion**—There are several difficulties in treating carcinomas of the floor of the mouth. Although the tumors are accessible and a superficial excision is immediately followed by a recurrence.

**RADIANTHERAPY**—External irradiation of these tumors contributes rapid diminution of the tumor and of the secondary infection. For this reason it appears advantageous as a preliminary step of the treatment but external irradiation alone seldom contributes permanent control of the lesion.

Peroral roentgentherapy is possible only in very few instances where a small tumor can be well enclosed within a rather narrow beam of radiations. In general however the tumors present a diffuse spread which does not lend itself to this form of treatment.

**CURETHERAPY**—Radium has been considered the treatment of choice of carcinoma of the floor of the mouth by most workers (Roux-Berger, Duenning, Quick, Gros). *Surface therapy* with the help of a molded apparatus is favored and has given reasonably good results in skilled hands. Melville described a technique of curettherapy based on the double application of a molded apparatus one intraoral the other submental the purpose of which was to irradiate as homogeneously as possible the area of the tumor. Although the three-year end results were very good he admitted a rather high incidence of healing complications and sequestration following this form of treatment. In general however when a surface application is to be used it is safer to follow this form of treatment by complementary interstitial irradiation.

**Interstitial chemotherapy** has been giving good results not only by the implantation of radium seeds but also by the implantation of radium element needles. The all important factors in both cases are the accurate distribution of the sources and the administration of a sufficient dose to the entire tumor area without damage or with the least possible damage to the surrounding structures. The most common complication of this treatment is radionecrosis of the soft tissue of the floor of the mouth and mandible which in itself is not necessarily fatal for patients may be permanently cured after elimination of fragments of the mandible. The complication is practically unavoidable how-

opathy The primary lesion may be found in an apparently innocent patch of sublingual leucoplakia

Left to themselves, most carcinomas of the floor of the mouth produce complications directly related to secondary infection and malnutrition

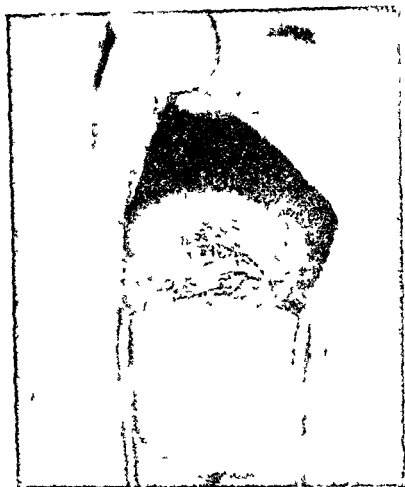


Fig. 10°—Lymphatic carcinoma of the floor of the mouth extending beyond the midline and over the lingual mucosa

### Diagnosis

There is as a rule very little difficulty in establishing a diagnosis of carcinoma of the floor of the mouth Examination should always be accompanied by a thorough digital palpation In most instances a biopsy is easily obtainable When there is no large ulceration the specimen may have to be taken with a scalpel on the indurated borders of the fissure An aspiration biopsy of suspected metastatic masses should always be done before treatment of the primary lesion is started in order further to establish, when possible, a positive diagnosis Negative aspirations of lymph nodes are not of course, conclusive

**Differential Diagnosis**—Few benign conditions of the floor of the mouth offer a problem of differential diagnosis A chronic inflammatory obstruction of the submaxillary or sublingual ducts produces a tumefaction of the floor of the mouth which may become indurated and displace the tongue upward In

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## CARCINOMA OF THE BUCCAL MUCOSA

## Anatomy

The cheeks, which form the lateral walls of the oral cavity, are formed by the buccinator muscle which is covered on its outer surface by a fairly thick layer of fat tissue and skin. Internally, the buccinator is covered by a smooth squamous epithelium which has considerably less surface than the cutaneous aspect of the cheek (Fig 193). The term buccal mucosa is now generally applied to that part of the oral mucous membrane which is connected with the cheek or buccal. It extends from the upper to the lower gingivobuccal gutters, where the mucous membrane reflects itself to cover the upper and lower alveolar ridges, and from the commissure of the lips to the ascending ramus of the mandible. The parotid duct opens at the level of the posteriosuperior quadrant of this surface at about the level of the second superior gross molar.

**Lymphatics**—The lymphatics of the buccal aspect of the cheek form collecting trunks which pierce the buccinator muscle and follow the direction of the facial vein, ending in the submaxillary and upper cervical lymph nodes. Any involved cervical nodes are usually situated in the prevascular group of the submaxillary region.

The lymphatics of the buccal mucosa may end in the buccinator group of the superficial facial nodes which are sometimes found over the outer surface of the buccinator muscle above a horizontal line extending from the buccal commissure to the lobule of the ear (Fig 176). Rarely some of them may end in the lower parotid nodes.

## Incidence and Etiology

The incidence of carcinoma of the buccal mucosa appears to be very variable according to regions and countries. In general, it occurs only a third or a fourth as often as carcinoma of the tongue and is found predominantly

ever, if the tumor has already invaded the bone but it can be avoided by proper treatment if the bone is not affected

**Treatment of the Cervical Adenopathy**—The best treatment of a submaxillary or cervical adenopathy is a radical neck dissection. A smaller number of patients with carcinoma of the floor of the mouth presenting metastases are eligible for a neck dissection for the following reasons

- 1 Healing of the primary carcinoma of the floor of the mouth requires more time, and in many instances the lesion develops into a radionecrotic ulceration which may simulate a failure of the treatment

- 2 Submaxillary metastases are often adherent to the mandible and in some instances are in direct continuity with the primary tumor

- 3 The submaxillary adenopathy is often bilateral

In spite of this, a therapeutic neck dissection is indicated in all cases where the operation is practicable for it offers the patient the only chance of a permanent recovery

An attempt to treat a metastatic adenopathy from a carcinoma of the floor of the mouth by means of roentgentherapy implies further irradiation of the mandible and, more often than not, it ends in a radionecrosis of the bone. External roentgentherapy is well able to sterilize a metastatic carcinomatous node under certain circumstances, but here, as in other instances, the contraindication to its use is based on the inability of the mandible to withstand the effects of the intraoral curietherapy plus external roentgentherapy, both given in doses sufficient to sterilize the primary and the secondary lesions

**PROPHYLACTIC NECK DISSECTION**—Taylor and Nathanson, in a study of 249 cases found that 90 per cent developed a metastatic adenopathy within a year. This development, of course, depends greatly on the relative success of the treatment of the primary lesion. Martin and Sugarbaker reported only eighteen patients (30 per cent) presenting subsequent metastasis of a group of fifty nine who did not have evidence of metastasis on admission. Although this percentage of metastases is less than that which is observed in carcinoma of the tongue, a prophylactic neck dissection may be justified in some instances. If the lesion approaches the midline a radical neck dissection on the same side as the lesion may be complemented by a submaxillary neck dissection on the opposite side

### Prognosis

The prognosis of carcinoma of the floor of the mouth is relatively favorable as compared with that of carcinoma of the tongue. Of a series of seventy seven patients treated, Regaud reported thirteen five year cures (17 per cent). Of a series of 103 treated patients Martin reported twenty two five year cures (21 per cent). In a series of sixty nine patients with carcinoma of the floor of the mouth and lower gingiva treated at the Holt Radium Institute of Manchester, thirty one (45 per cent) remained well three years after treatment by a double mold technique of curietherapy (Melville). The prognosis in those patients who do not present a metastasis on admission is twice as favorable as that in the patients without an adenopathy

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## CARCINOMA OF THE BUCCAL MUCOSA

## Anatomy

The cheeks, which form the lateral walls of the oral cavity, are formed by the buccinator muscle which is covered on its outer surface by a fairly thick layer of fat tissue and skin. Internally, the buccinator is covered by a smooth squamous epithelium which has considerably less surface than the cutaneous aspect of the cheek (Fig 193). The term buccal mucosa is now generally applied to that part of the oral mucous membrane which is connected with the cheek or buccal. It extends from the upper to the lower gingivobuccal gutters, where the mucous membrane reflects itself to cover the upper and lower alveolar ridges and from the commissure of the lips to the ascending ramus of the mandible. The parotid duct opens at the level of the posteriosuperior quadrant of this surface at about the level of the second superior gross molar.

**Lymphatics**—The lymphatics of the buccal aspect of the cheek form collecting trunks which pierce the buccinator muscle and follow the direction of the facial vein, ending in the submaxillary and upper cervical lymph nodes. Any involved cervical nodes are usually situated in the prevascular group of the submaxillary region.

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## Incidence and Etiology

The incidence of carcinoma of the buccal mucosa appears to be very variable according to regions and countries. In general, it occurs only a third or a fourth as often as carcinoma of the tongue and is found predominantly

in patients of a more advanced age, as an average than those who present other forms of oral carcinomas. The ratio of males to females has been reported as high as 10 to 1 by Richards, who found an average age of 64 years.

The use of tobacco particularly for chewing appears to have an important role in the etiology of these tumors. It is our impression that in some rural areas of the United States carcinoma of the buccal mucosa may be even more frequent than carcinoma of the tongue, and, admittedly, the chewing of tobacco may play a role in this difference (Friedell and Rosenthal).

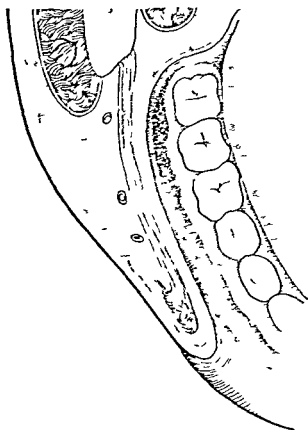


Fig. 1 —Anatomic sketch of the buccal mucosa showing close relationship of the mucous membrane and the muscle.

In southern India the incidence of carcinoma of the oral cavity is rather high. ILLIS observed 346 cases, while only six carcinomas of the breast were observed at the same time, and this in a part of India where the purdah system was not in effect and where women came freely to the hospital for diagnosis. These tumors occur in younger male individuals, the peak age incidence being at least one decade below that found in the United States. The incidence of carcinoma of the oral cavity has been reported as constituting 35 to 40 per cent of all forms of cancer in southern India (Snijders); the most frequently affected site being the buccal mucosa. ORR reported a series of 669 cases of carcinoma of the oral cavity in natives of south-east India (Travancore) of which 296 (45 per cent) arose on the buccal mucosa. DAVIS observed that carcinoma of the buccal mucosa is also common in the Philippine Islands but



is more frequently found in women. These curious phenomena have been attributed to the widespread habit of chewing betel nut (or buyo). This habit is prevalent among the natives of India, Ceylon, Malay, Asia, Thailand, Indo-China, and Philippine Islands, but the incidence of carcinoma of the oral cavity is not the same in all places where betel nut chewing is common. These variations have been explained in terms of changes in the ingredients or in the fashion of chewing (Oll). Khanolkar found that the incidence of carcinoma of the oral cavity was even greater in some instances in regions of India where the habit of betel chewing does not exist. It is possible that the betel chewing only supplements bad oral hygiene and that dietary factors may be overwhelmingly more important. It may be significant, however, that Khanolkar reported a greater number of carcinomas of the glossopharyngeal sulcus and base of the tongue among the patients observed by him, while, as stated before, other authors have found a great majority of carcinomas of the buccal mucosa among the betel chewers.

The quid consists of areeka nuts (betel palm), slaked lime, tobacco, spices (cardamom and nutmeg), and buyo leaves from the *Piper betel* plants (Hueper) and is carried between the lower teeth or gums and the buccal mucosa. The lime sweetens the bitter taste of the leaves which contain essential oils, the betel nut is rich in tannic acid. The chewing of these ingredients results in the formation of a bright red dye. The tobacco included in the quid may well play an important role in carcinogenesis (Friedell).

### Pathology

**Gross Pathology**—Carcinomas which arise on the buccal aspect of the cheeks develop rather frequently from a pre-existing area of leucoplakia. In fact, except for carcinomas of the tongue, there is no other lesion of the oral cavity which is so frequently associated with or preceded by a leucoplakic patch. The lesions most commonly arise on that part of the buccal mucosa which lies against the third lower molar, but also may arise from the middle of the buccal area against the occlusal line of the teeth and from the neighborhood of the commissure of the lips.

Grossly there are three distinct types: the exophytic, the ulcerating, and the verrucous.

The *exophytic* papillary growths are usually soft and whitish in appearance. They are commonly associated with and preceded by leucoplakia and usually become thick but not necessarily extensive. They are more commonly found at the level of the buccal commissure (Fig. 194).

The *ulcerating* lesions are not as common but often present a deep excavation with diffuse surrounding infiltration. They invade the buccinator muscle rather early in their development and also extend to the anterior pillar of the soft palate and to the lower alveolar ridge. Actual invasion of the bone is not infrequent. Extension to the pharyngomaxillary fossa occurs easily from posteriorly situated lesions. The ulceration may extend through the entire thickness of the cheek to ulcerate the skin. When the buccal commissure is involved, the lesion may enlarge the opening of the mouth.

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The use of tobacco, particularly for chewing, appears to have an important role in the etiology of these tumors. It is our impression that in some rural areas of the United States carcinoma of the buccal mucosa may be even more frequent than carcinoma of the tongue, and, admittedly, the chewing of tobacco may play a role in this difference (Friedell and Rosenthal).

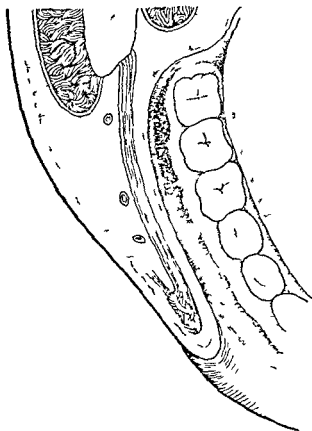


FIG. 10.—Anatomic sketch of the buccal mucosa showing close relationship of the mucous membrane and the muscle.

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The *verrucous* type of carcinoma of the buccal mucosa is a clean, soft, superficial, granulating lesion with little secondary infection or ulceration and with practically no infiltration in depth. These lesions spread considerably in surface and may extend to the hard palate and lower alveolar ridge. In very advanced cases the lesion becomes thickened and secondarily infected (Fig 195).

**METASTATIC SPREAD** According to Richards, only about half of all carcinomas of the buccal mucosa present a metastasis during their development. Actually, the percentage of metastases found in any series will depend considerably on the number of verrucous type of carcinomas which are included, for these last very seldom metastasize. The ulcerating and exophytic types metastasize with the usual frequency of all carcinomas of the oral cavity. Metastases more often appear in the submaxillary region, but rarely in the parotid gland group of lymph nodes (Fig 198). Distant metastases occasionally occur, as in other carcinomas of the oral cavity. Brand reported four cases with distant metastases in ten cases of carcinoma of the buccal mucosa that came to autopsy.

**Microscopic Pathology** Most carcinomas of the buccal mucosa are rather well differentiated. Transitional cell carcinomas and lymphoepitheliomas do not arise in this area of the oral cavity.

It is worthy of special note that in the verrucous type of carcinoma repeated biopsies may reveal only hyperkeratinization, hyperplasia, and chronic inflammation. After multiple trials, and sometimes at the expense of time lost, the diagnosis of carcinoma may be reached after the disease has made some further progress.

Microscopically, long fingers of well differentiated squamous epithelium dip deeply into the tissues but maintain their basement membrane. As the process becomes more advanced, considerable inflammation is present just beneath this basement membrane. The tumor insinuates itself into the soft tissues of the cheek and can extend to the surface, where it may ulcerate. No matter how extensive or how deeply invasive, it maintains its extremely well differentiated pattern.

### Clinical Evolution

The onset of carcinomas of the buccal mucosa is usually insidious. Frequently the lesion has infiltrated sufficiently to produce *trismus* by the time the first examination is made. A submaxillary *adenopathy* is sometimes the first clinical symptom, and *bleeding* may be present in variable degrees. *Pain* is very intense in the ulcerating forms but may not appear at all in extensive stages of the verrucous type of carcinoma.

Exophytic lesions grow to be considerably bulky and may interfere with mastication. Ulcerating lesions can involve the entire surface of the buccal mucous membrane and be surrounded by indurated, edematous tissues. In these cases there is usually a marked amount of *secondary infection*. Left to themselves, the exophytic and ulcerating lesions of the buccal mucosa invade and destroy the entire cheek and present metastases to the submaxillary and



Fig. 101.—Exophytic type of carcinoma of the buccal mucosa. (Courtesy of Dr. Simeon T. Cantrell, Tumor Institute, Swedish Hospital, Seattle, Wa.)



Fig. 102.—Extensive verrucous type of carcinoma of the buccal mucosa in an elderly patient.

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upper cervical regions. The general condition of the patient is affected because of the secondary infection and inability to masticate. Distant metastases are seldom found.

The verrucous type of carcinoma produces practically no functional defect and is accompanied by very little induration, and in a rapid examination its extension to the adjacent structures may not be evident. The advanced verrucous carcinoma may produce considerable destruction of the upper alveolar ridge and mandibular bone terminating fatally without even metastasizing to the submaxillary region.

### Diagnosis

There are a few benign conditions of the buccal mucosa and they offer little difficulty in the differential diagnosis. Mucous cysts are usually multiple, small, and separated by areas of normal mucous membrane. Leucoplakia is frequently found, particularly around the commissure of the lips, usually in the form of an isolated patch of raised whitish mucous membrane. Although these areas of leucoplakia may disappear upon improving the hygienic conditions of the mouth, they should be excised as a prophylactic measure, because some areas of leucoplakia which appear benign may show evidence of neoplastic degeneration on microscopic examination.

The verrucous type of carcinoma of the buccal mucosa clinically appears as a benign condition because of its lack of ulceration, secondary infection and symptomatology. In addition, repeated biopsies may contain nothing but hyperkeratinization, hyperplasia and chronic inflammation. It is important to remember that in spite of this the lesions will behave with a rather malignant local character although they seldom metastasize. After several local excisions and recurrences, the diagnosis of well differentiated epidermoid carcinoma is invariably finally established.

Salivary and mucous gland tumors are found around the orifice of the parotid duct and are generally well defined nonulcerating slowly growing tumors. The decision to excise or not to excise these tumors will depend upon the age of the patient, the rapidity of growth, the presence of ulcerations, etc. Histopathology is characteristic (see Tumors of the Salivary Glands page 618).

### Treatment

There is a great partiality in respect to the treatment of carcinomas of the buccal mucosa. Good results may be obtained in early cases both by surgical excision and by radiotherapy. The cure of tumors which have already invaded adjacent structures will depend greatly on the method of approach.

ROENTGENTHERAPY.—External roentgentherapy has been used as a preparatory measure before interstitial curietherapy or surgical excision is carried out. As such, roentgentherapy seems to be of unquestionable value but used alone as a curative measure, it gives inconstant and not sufficiently good results to justify its systematic and exclusive use. Peroral roentgentherapy is practical only in limited lesions of the posterior half of the buccal mucosa and in particular those which have already invaded the anterior pillar of the soft

palate. In these cases, a combination of external and perioral irradiation may be but is not often sufficient to control the lesion.

**CURATIVE**—External irradiation by means of a "radium pack" of several grams of radium has no particular advantage over external irradiation by means of the average equipment of roentgentherapy. In fact the external irradiation with radium is, of necessity, more diffuse because of the relative proximity of the source of radiations and the relatively large size of the source area. This diffuse irradiation is particularly disadvantageous when applied to the oral cavity. In addition, experience has shown that the results obtained are not better than those of roentgentherapy.



Fig. 196.—Surgical specimen of a radical excision of a verrucous carcinoma of the buccal mucosa. Note the mandible, submaxillary gland, and other structures included in the specimen.

The best results in the treatment of carcinoma of the buccal mucosa appear to have been obtained by the use of interstitial curietherapy with radium element needles. Richards has used this form of treatment in conjunction with external and perioral roentgentherapy with good results. The insertion of radium element needles allows a concentrated but sufficiently homogeneous irradiation to eradicate a limited carcinoma without damage to the adjacent structures. This type of irradiation cannot be applied to lesions which have already invaded the upper or lower alveolar ridge or the anterior pillar of the soft palate. It may be very successful in all lesions which are sufficiently separated from those structures to avoid untoward effect. Martin advocates the use of radon seeds which may give equally good results but requires considerably greater skill and is more often followed by late radionecrosis.

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The exophytic type of lesion is particularly suitable for interstitial chemotherapy. Seldom, however, are the ulcerating lesions sufficiently well delimited to justify its use. The verrucous type of carcinoma can also be treated by interstitial radiation whenever it is found limited to the buccal mucous membrane, but these lesions are usually too widespread to be controlled by this form of treatment. Interstitial radiation of the buccal mucosa has the added advantage that its failure does not necessarily imply the failure to cure the disease. As soon as a recurrence is detected following interstitial radiation, a radical excision can be carried out just as well and perhaps better than if it had been done in the first place. Recurrences not being the rule, this sequence is well justified.

**SURGERY**—Early accessible lesions of the buccal mucosa may be successfully excised. In some instances a wide excision of the buccal mucosa may be followed by a skin graft. These limited excisions, however, are only justified in the very early lesions and are still often followed by a recurrence.

For moderately advanced ulcerating lesions of the buccal mucosa and for all such lesions which have already invaded the lower alveolar ridge or which have metastasized to the submaxillary region, the wisest and most successful procedure is probably a radical en bloc excision of the primary lesion and its adenopathy. An atypical form of radical neck dissection which includes resection of part of the mandible and some other oral structures is known as the Bloodgood operation. It is usually applied with appreciable success for radical treatment of carcinomas of the buccal mucosa or of the lower alveolar ridge. The operative mortality in the past has been rather high. In a series of fifty-five patients subjected to this type of operation by Ellis Fischel, eleven (20 per cent) died postoperatively (Keyes). When the tumor has invaded the soft palate, the upper alveolar ridge, or the pterygoid fossa, even the most radical operation is bound to terminate in failure. Verrucous carcinomas which have invaded and destroyed the mandible, however, may be successfully treated by this type of surgery (Fig 196). Lengthy and tedious plastic repair is sometimes necessary following this radical excision, and the cosmetic result, although not perfect, may eventually be quite satisfactory (Fig 197). In spite of any disadvantages, however, this operation is well justified when applied to the aforementioned lesions which are not curable by any other means.

### Prognosis

**Classification**—Richards advocates the classification of cases of carcinoma of the buccal mucosa into four stages as follows:

- Stage I—Lesions measuring up to 1.5 cm without involvement of adjacent structures
- Stage II—Lesions larger than 1.5 cm without involvement of adjacent structures
- Stage III—Involvement of adjacent structures (alveolar ridge, anterior pillar, skin)
- Stage IV—Widespread involvement, far advanced

This classification offers some basis for a prognosis in the absence of an adenopathy. When an adenopathy is present, however, the relative evaluation of the prognosis is too complicated and of little use.



Fig 197—Patient treated for a carcinoma of the buccal mucosa by a radical surgical excision  
satisfactory cosmetic result



Fig 198—Metastatic carcinoma of the submaxillary region from a primary lesion in the buccal  
mucosa. Note small satellite nodule

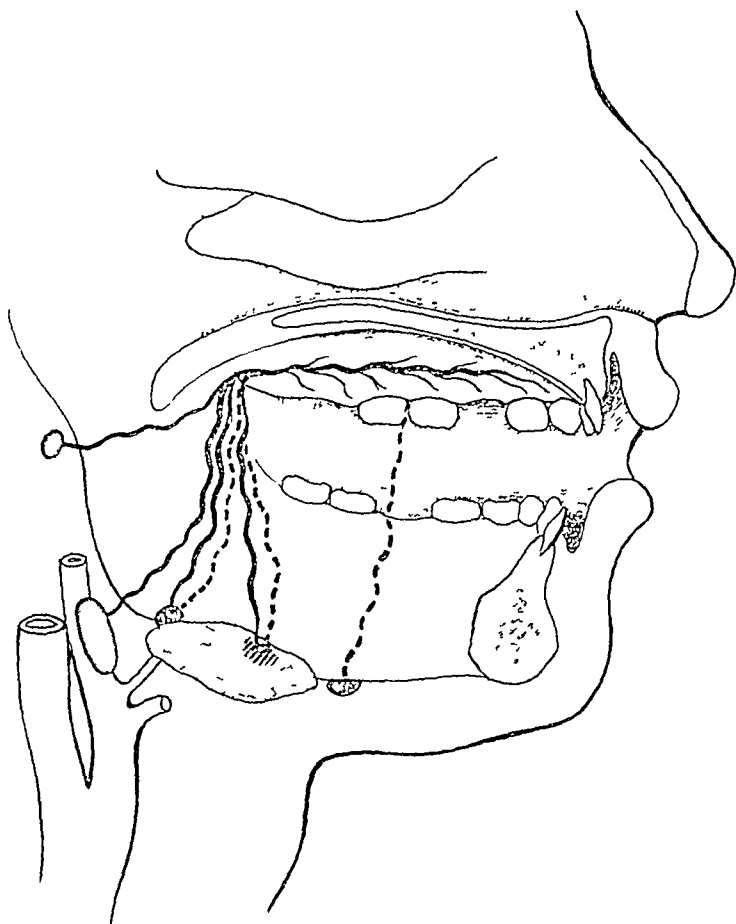


Fig 199.—Sketch of the lymphatics of the upper gingiva ending in submaxillary or jugular lymph nodes and rarely in the retropharyngeal nodes

The prognosis of ulcerating lesions of the buccal mucosa is rather poor, but that of verrucous carcinoma is very good. The prognosis of exophytic lesions will depend greatly on the stage of their development. Richards reported a series of thirty nine treated patients with fifteen (38 per cent) well five years or more. Dividing his cases according to stages, Richards found a definite means of prognosis varying from 94 per cent in Stage I to 12 per cent in Stage IV. Martin reported a series of ninety nine treated patients of whom twenty eight (28 per cent) were living and well five years after treatment.

A series of fifty five radical operations (Bloodgood type) applied to carcinomas of the lower gingiva and other lesions by Ellis Fischel (Keyes) resulted in thirteen five year survivals (24 per cent).

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## CARCINOMA OF THE UPPER GINGIVA

### Anatomy

The upper gingiva is formed by the tissues which cover the alveolar ridge of the upper maxilla. It is formed by fibrous tissue which is continuous with the periosteum of the bone and by a stratified squamous epithelium similar

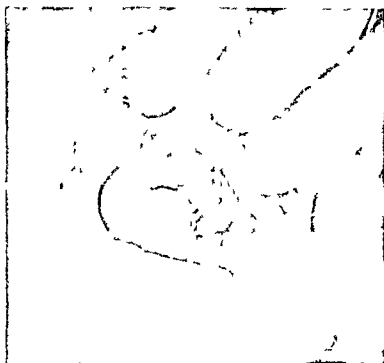


Fig 200—Typical papillary carcinoma of the upper gingiva

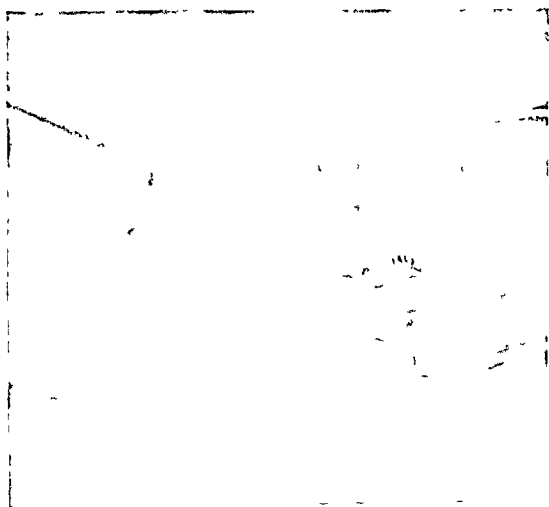


Fig 201—Verrucous type of carcinoma of the upper gingiva



Fig 202—Rare epidermoid carcinoma of the upper gingiva at the midline

to that of the rest of the oral cavity. This mucous membrane is rather thick and does not contain glands. Around the neck of the teeth the gingiva forms an overlapping collar. The upper gingiva extends only a few millimeters medial to the neck of the teeth. Laterally it is considerably more extensive. The epithelium that covers it is reflected upon itself deep in the gingivobuccal and gingivolabial gutters to become the buccal mucosa and the mucous membrane of the upper lip.

**Lymphatics**—ROUVIERE divides the lymphatics of the upper gingiva into a lateral or external network and a medial or internal network. The lateral group of lymphatics pierces through the upper insertions of the buccinator muscle, follows the facial vein to the submaxillary region, and ends in submaxillary lymph nodes. The medial group of lymphatics follows an antero-posterior direction and joins the lymphatics of the hard and soft palates behind the dental arch. From there on they form part of the same group but often end in lymph nodes of the anterior jugular chain. More rarely they will end in the submaxillary and retropharyngeal lymph nodes (Fig. 199).

### Incidence and Etiology

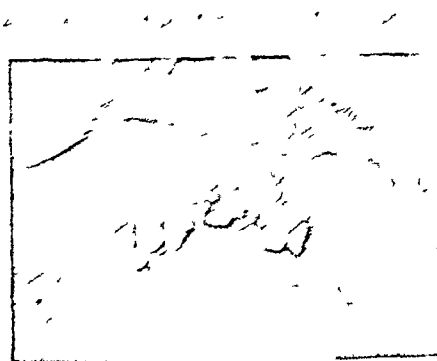
Carcinomas of the upper gingiva are not as common as those of the lower gingiva. They are usually reported together with carcinomas of the maxillary antrum under the heading of cancer of the upper jaw, and for this reason it is difficult to estimate the approximate incidence. They occur predominantly in men in the fifth and sixth decades of life.

Ill fitting dentures, carious teeth, the use of tobacco and syphilis have been incriminated as causative factors in this as in other forms of cancer of the oral cavity. Without denying the possible role of poor oral hygiene and chronic irritants it should always be borne in mind that these findings may be coexistent.

### Pathology

**Gross Pathology**—Carcinomas of the upper gingiva are usually papillary, presenting deep crevices and a leathrized surface. They usually develop over the molar and premolar areas and very rarely on the anterior midline (Fig. 202). Extension toward the hard palate is often submucous, giving an adjacent smooth tumefaction which seldom extends beyond the midline. Lateral spread to the upper gingivobuccal gutter by extension of the ulceration is much more common. Extension into the floor of the maxillary antrum through the alveoli usually occurs earlier in those patients who still have their teeth, inasmuch as disease loosens the teeth and the tumor can easily spread through the alveolar canal. Invasion of the soft structures of the cheek and upper lip is only seen in very advanced cases. In general the soft structures are merely displaced.

**METASTATIC SPREAD**—As a general rule carcinomas of the upper gingiva metastasize to the submaxillary lymph nodes. Very seldom they metastasize to the nodes of the upper cervical region. The chances of metastatic spread increase after invasion of the upper gingivobuccal gutter and buccal mucosa.



membrane Thirty eight per cent of the cases studied by Taylor and Nathan son presented lymph node metastases The larger the size of the lesion and the lesser the differentiation of the tumor, the greater the chances of metastatic implants Bilateral metastases are very seldom seen It must be noted that verrucous carcinomas seldom, if ever, metastasize

**Microscopic Pathology**—Almost all carcinomas of the upper jaw are well differentiated Verrucous carcinomas which are more frequently found on the buccal mucosa and lower jaw are also observed on the upper gingiva (Fig 201) Of all melanomas of the oral cavity, the greater number are found on the upper gingiva, but compared with other tumors of this area, they are very rare Very rarely, sarcomas arising from the upper maxilla may ulcerate the upper gingiva On microscopic examination some of these tumors will be typical but others may be difficult to differentiate from an embryonic type of carcinoma Mucous and salivary gland tumors, which occur more often on the hard palate, may arise near the medial limits of the upper gingiva or on its lateral aspect These tumors are microscopically typical and may present a mixed tumor appearance or a cylindromatous arrangement or may present themselves as adenocarcinomas (see Tumors of the Hard Palate, page 306)

### Clinical Evolution

Carcinomas of the upper gingiva are usually first noticed because of their interference with the fitting of a denture or because of ulceration around teeth For these reasons the dentists are often first consulted In general, there is a friable papillary outgrowth extending over the middle or posterior third of the upper gingiva (Fig 200) As a rule there are few other symptoms except otalgia when there is coexistent secondary infection Spontaneous bleeding may also be observed Trismus is only found in very advanced cases

A submaxillary adenopathy is usually found in the moderately advanced cases particularly when disease has invaded laterally Upper cervical metastases are sometimes observed, but distant metastases are very uncommon Death often occurs from complications such as hemorrhage and bronchopneumonia

### Diagnosis

Carcinomas of the maxillary antrum which develop on the infrastructure of the superior maxilla may extend to the upper gingiva and become ulcerated therein It may be impossible in some cases to establish with certainty the gingival or the nasal point of departure of an epidermoid carcinoma In the majority of cases however the carefully recorded details of the history and the physical findings will speak eloquently enough for one or the other point of origin Primary carcinomas of the maxillary antrum usually produce a smooth, nonulcerated tumefaction in the upper gingivobuccal gutter, and loosening of the teeth usually precedes the development of a gingival ulceration In addition nasal discharge bleeding or nasal obstruction may have preceded the appearance of a tumefaction or ulceration of the upper gingiva

In carcinomas of the upper gingiva on the other hand, the loosening of the teeth occurs after the growth has eroded around them the ulceration is



present from the beginning and is usually wider, and the extension to the antrum occurs late. In addition, the microscopic examination of a biopsy specimen will reveal a rather undifferentiated carcinoma in the case of those



Fig. 203—Peripheral giant-cell tumor of the upper gingiva



Fig. 204—Fibrous epulis of the upper gingiva

arising in the antrum, while, as a general rule, those arising on the gingiva are rather differentiated keratinizing carcinomas. The point of origin, however, cannot be determined on a microscopic basis.

membrane. Thirty eight per cent of the cases studied by Taylor and Nathanson presented lymph node metastases. The larger the size of the lesion and the lesser the differentiation of the tumor, the greater the chances of metastatic implants. Bilateral metastases are very seldom seen. It must be noted that verrucous carcinomas seldom, if ever, metastasize.

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A submaxillary adenopathy is usually found in the moderately advanced cases particularly when disease has invaded laterally. Upper cervical metastases are sometimes observed but distant metastases are very uncommon. Death often occurs from complications such as hemorrhage and bronchopneumonia.

### Diagnosis

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the diseased gum Fibrous epulis is usually a pedunculated, nonulcerated, rubbery growth (Fig 203) These benign growths may be present in both young and aged people In children, the differential diagnosis of benign lesions will be simplified because of the age (Fig 205) Other conditions of the upper gingiva, such as hypertrophic gingivitis, are easily recognized

Malignant melanomas occur but rarely in the oral cavity and more often arise from the anterior and middle thirds of the upper gingiva (Fig 207) These tumors will be recognized by their typical dark pigmentation (Baxter) Primary central tumors of the upper jaw such as ameloblastomas, dentigerous cysts, primary tumors of the antrum or nasal fossa, sarcomas of the bone, and metastatic carcinomas of the upper maxilla may produce a tumefaction of the upper gingiva and a loosening of the teeth In later stages, they result in a wide ulceration of the oral cavity The differential diagnosis of the point of origin is not always possible in these cases but the history, the physical findings, the clinical sequence of events, and the biopsy should help to do this



FIG. 207 Melanoma of the upper gingiva (Courtesy of Dr H. A. Baxter, Montreal, Can.)

### Treatment

**RADIOTHERAPY**—As it has been stated, the majority of the carcinomas of the upper gingiva are well-differentiated tumors which metastasize late or are carcinomas of the verrucous type which do not metastasize at all. Although external irradiation can sterilize these lesions, it is not infrequently followed by a recurrence, while a skillful surgical excision of these tumors is usually successful. Perioral roentgentherapy is feasible in limited growths which can be included in a circular field of irradiation. Administration of roentgentherapy in this manner, however, over an area of the mucous membrane which lies in contact with the bone, is often followed by radionecrosis.

**Roentgenographic Examination**—Roentgenographic examination of the superior maxilla will be helpful in establishing the extent of bone destruction as well as that of the invasion of the maxillary antrum. In primary tumors of the upper gingiva, the maxillary antrum may be cloudy due to neighboring edema, but the bone destruction is limited to the alveolar border. In carcinoma of the antrum, the bone destruction is in general more extensive.

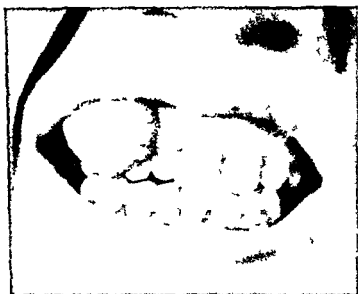


FIG. 9.—Film of the upper gingiva in a young girl. (Courtesy of Dr. F. J. Lantz, Instituto de Radium, Havana, Cuba.)



FIG. 10.—Carcinoma of the maxillary antrum invading the upper gingiva and hard palate. (Courtesy of Dr. Simeon T. Cantel, Tumor Institute, Sweet's Hospital, Seattle, Wash.)

**Differential Diagnosis**—There occur in the upper gingiva several benign growths which can be easily differentiated from malignant tumors. Peripheral giant cell tumors (epulis) are usually shiny, grow around the teeth with a varied consistency, and have no ulceration (Fig. 204). Ulceration and secondary infection occurs nevertheless when teeth have been extracted from

(25 per cent) Reports of other authors (Hautant, Ohngren) include lesions of the maxillary antrum and ethmoid and cannot be properly evaluated for results in carcinoma of the upper gingiva

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## CARCINOMA OF THE LOWER GINGIVA

### Anatomy

The lower gingiva is formed by the soft tissues which cover the alveolar ridge of the mandible The mucous membrane of the floor of the mouth extends laterally and forward to cover the inner aspect of the alveolar process where it becomes continuous with the periosteum of the alveoli The mucous membrane joins between the teeth with that which covers the outer aspect of the alveolar ridge, and when teeth are not present, the mucous membrane entirely covers the free border of the mandible Laterally the mucous membrane extends over the outer surface and reflects upon itself in the gingivobuccal and gingivolabial gutters where it joins with the buccal and labial mucous membranes (Fig 208) At the level of the alveolar ridge, the mucous membrane is rather thick with underlying rich connective tissue, and, unlike the mucous membrane of the rest of the oral cavity, it is not provided with glands

**Lymphatics**—Rouvière divides the lymphatics of the lower gingiva into an external or lateral network and an internal or medial network The lymphatics of the lateral aspect of the lower gingiva gather into several trunks which pass through the insertions of the buccinator muscle and follow the facial vein to end in the submaxillary lymph nodes The lymphatics of the region of the incisors may end in the submental lymph nodes The medial lymphatics pass through the mylohyoidian muscle and end predominantly in the submaxillary nodes which are found in front of the submaxillary gland Others follow an opposite direction, passing outside of the styloglossus muscle and inside of the digastric muscle, and end, for the most part, in the subdigastric group of lymph nodes (Fig 209)

and sequestration of the bone. If perioral roentgentherapy is to be used, its role should be only a complementary one after external irradiation. Roentgentherapy finds its best indications in early lesions (not over 3 cm in diameter) which are exophytic in type and which have a moderate degree of histologic differentiation. In these cases a wide surgical excision is still possible if a recurrence manifests itself.

Application of radium molds for surface curietherapy is not as successful in the treatment of carcinomas of the upper gingiva as it is in those of the lower gingiva for the same reasons referred to previously in dealing with perioral roentgentherapy.

**STRECK —** A wide surgical excision of tumors of the upper gingiva which have invaded the lower structure of the maxilla is often successful. This treatment usually implies a resection of parts of the hard palate and maxillary bone but the extent of the resection will depend of course, on the extent of the disease. As a general rule the operation can be done through the opening of the mouth. In more advanced cases however it may be necessary to enlarge the opening by making an incision around the alar nasi and midline of the upper lip. These resections do not need to extend to the floor of the orbit and consequently change very little the symmetry of the face. **LECTOSURGERY** is preferred by many surgeons (Ohnuma). The resections often result in a large perforation of the hard palate into the nasal fossa and maxillary antrum which must be occluded by especially fitting prosthetic appliances (Aclermann).

It has been the custom in the past to follow this atypical resection of the maxilla by an intracavitary application of curietherapy. The success of this form of treatment however depends on the wide excision of the tumor. Furthermore, it is unlikely that if residual tumor remains it can be sterilized by an application of radium because the radium cannot be directed to the residual tumor, it will be unequally distributed throughout the region and carcinomas of the upper gingiva are usually not very radiosensitive. In those tumors of the upper gingiva which have invaded beyond the midline or those which have already infiltrated the buccal mucosa the chances of success by a surgical resection are considerably diminished. Now and then however a heroic approach by excision or destruction by endothermy of large areas of the cheek and bone may be successful.

When a cervical adenopathy is present, a radical neck dissection is indicated. In the absence of a palpable cervical adenopathy an expectant attitude is justified for only a small percentage of these patients will develop a metastasis after the primary lesion has been controlled.

### Prognosis

An adequate therapeutic approach to these cases will contribute a rather good percentage of results. In a series of forty seven patients treated at the Memorial Hospital of New York, Martin reported twelve five year survivals

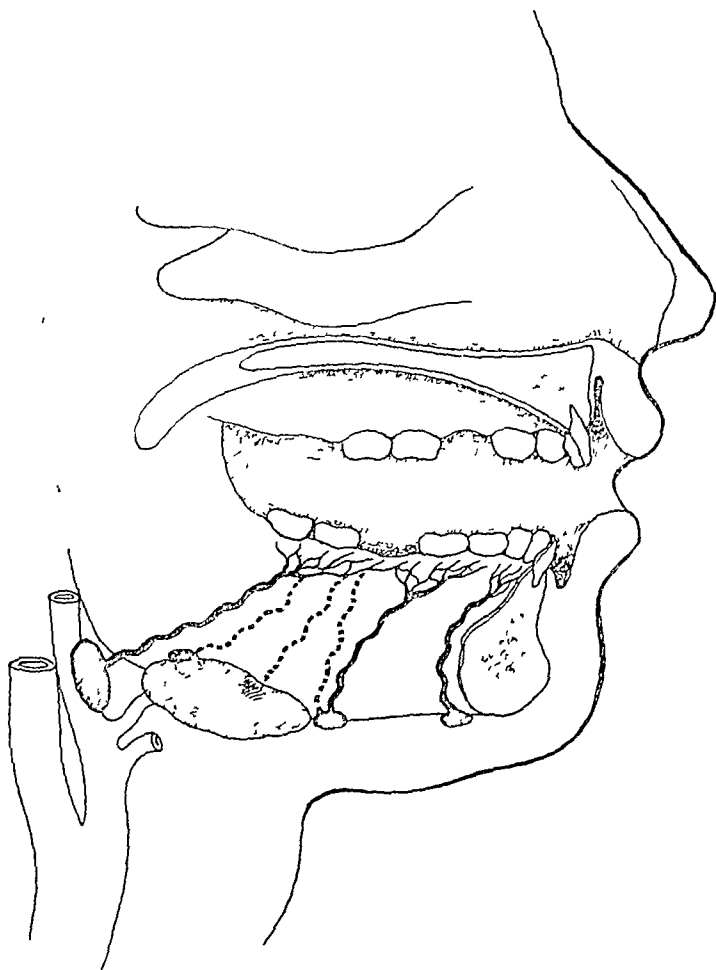


Fig. 209 - Anatomic sketch of the medial and lateral lymphatics of the lower jaw leading to the submental, submaxillary and sublingual lymph nodes

### Incidence and Etiology

In a series of 1,329 patients with carcinoma of the oral cavity admitted and treated at the Radium Institute of Havana, Cuba, during a period of twenty one years seventy two cases (5.4 per cent) were found to originate from the lower gingiva. Carcinomas of the lower gingiva are predominantly found in men at an older age than is usual for other forms of cancer of the oral cavity and are very rarely found in individuals under 40 years of age.

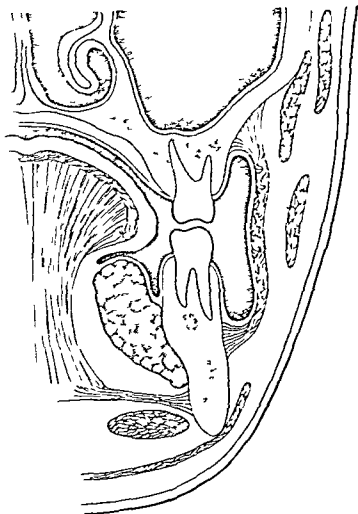


FIG. 208.—Frontal section of the lower and upper jaws illustrating the medial and lateral contours of the lower gingiva and its close relationship to the floor of the mouth and sublingual gland as well as to the buccal mucosa and buccinator muscle.

### Pathology

**Gross Pathology**—Carcinomas of the lower gingiva usually arise in the molar area or posterior third of the dental arch. They are sometimes found in the premolar or middle third area but are very rarely seen to arise in the anterior third or midline area. They may arise from a previously existing patch of leucoplakia or may be associated with leucoplakia of the oral cavity.

Grossly the most common forms of carcinoma of the lower gingiva can be divided into three types: exophytic, ulcerating and verrucous. The *exophytic*



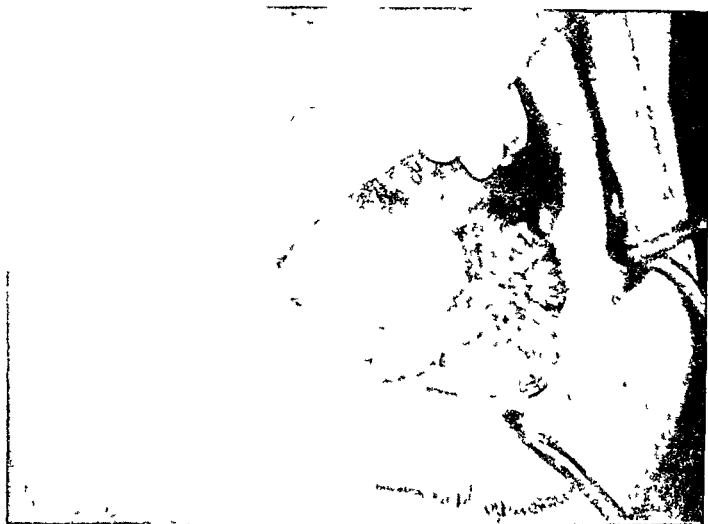


Fig 212—Typical extensive verrucous carcinoma of the lower gingiva. Superficial biopsy in such cases may not reveal carcinoma. (From Burford W N, Ackerman L V and Robinson H G B. *Am J Orthodontics and Oral Surg* 1944.)



Fig 213—Roentgenogram of the same patient illustrated in Fig. 212 showing the extensive bone destruction.

type of lesion is a cauliflower like outgrowth which is seldom confined to the gingiva. This lesion bleeds easily and has a tendency to spontaneous necrosis (Fig. 210). The *ulcerating* type of growth is usually accompanied by extensive



Fig. 210. Typical exophytic carcinoma of the lower gingiva. (Courtesy of Dr. Simon T. Cantrell, Tumor Institute, Southern Illinois University, Springfield, Ill.)



Fig. 211. Typical exophytic carcinoma of the lower gingiva. (Courtesy of Dr. Simon T. Cantrell, Tumor Institute, Southern Illinois University, Springfield, Ill.)

invasion of the bone with extension of the tumor (Fig. 211). The tumor is a type of carcinoma which is characterized by a proliferation of epithelial cells with a tendency to invade the underlying connective tissue and bone of the jaw (Figs. 212, 213 and 214).

Distant metastases were found in five of fourteen cases of carcinoma of the lower gingiva which came to autopsy at the Memorial Hospital in New York (Martin)

**Microscopic Pathology**—The great majority of carcinomas of the lower gingiva are epidermoid and, as a rule, are rather differentiated. Melanocarcinomas and adenocarcinomas have been observed rarely. It is worthy of note that in the verrucous type of carcinoma, a single biopsy may only show hyperkeratinization, hyperplasia, and chronic inflammation, and that only on repeated biopsies or on examination of a surgical specimen may a definite diagnosis of epidermoid carcinoma be made. Microscopically it is characterized by long fingers of squamous epithelium extending deeply into the tissues but maintaining its basement membrane (Fig 214). It maintains a well-differentiated pattern throughout.

### Clinical Evolution

Generally, carcinomas of the lower gingiva are first noticed because they interfere with the proper fitting of a denture or because of bleeding on mastication. The dentist is most often consulted as to these difficulties and consequently he holds a great part of the responsibility for the early diagnosis. There is often a history of extraction of teeth and of surgical incisions for a suspected alveolar abscess before a correct diagnosis is established. There may be a spontaneous *bleeding*, but this is usually connected with exophytic tumors. *Otalgia* on the same side as the lesion often accompanies secondary infection. *Trismus* is sometimes observed particularly when the tumor develops posteriorly. Severe pain often accompanies the ulcerating type of lesion which has developed extensive invasion of the bone. In verrucous carcinomas there may be a remarkable absence of all symptoms in spite of the extension of the tumor.

On examination of the gingiva, the most common lesion is an exophytic rubbery growth extending to the floor of the mouth and to the gingivobuccal gutter. Less commonly the lesion is ulcerated exposing the mandible and accompanied by considerable induration and infiltration of the surrounding tissues. Superficial, nonulcerated and nonsecondarily infected lesions of the verrucous type usually extend to adjacent structures. They have a typical granular appearance and their exact limits may be difficult to establish (Fig 216).

An outside tumefaction of the lower portion of the cheek with adherence to and ulceration of the skin is not uncommonly found (Fig 218). Enlargement of the submaxillary lymph nodes is present in more than half of the cases and, although not always, they are most often metastatic. The submaxillary tumefaction may represent direct extension of the tumor, but because of ulceration and secondary infection there may be inflammatory enlargement of the lymph nodes and of the submaxillary gland.

Death usually occurs in unsuccessfully treated cases or in post-treatment recurrences and is usually caused by complications such as hemorrhage and bronchopneumonia. Distant metastases, although sometimes found, are seldom directly responsible for the death.

Laterally, tumors of the lower gingiva easily spread to the subcutaneous fat and skin of the cheek producing an outside tumefaction which is continuous with the primary growth, and then they may rapidly break through the skin. Medially these tumors often extend to the floor of the mouth where they invade the sublingual tissues but only exceptionally do they succeed in spreading directly to the submaxillary fossa. Posteriorly the spread of these tumors to the retromolar area puts them in the region of the anterior pillar of the soft palate from where they can extend to the pterygomaxillary fossa. In depth they extend through the alveoli to the center of the mandible producing, at times wide areas of bone destruction (Figs 213 and 217). They can also extend along the periosteum for a considerable distance unsuspected clinically and radiographically.



Fig 214—Photomicrograph of a typical verrucous carcinoma of the lower gingiva showing long fingers of deeply invading well differentiated squamous epithelium. The basement membrane is intact.

**METASTATIC SITE**—A majority of cases with carcinoma of the lower gingiva develop an adenopathy sometime during their course. This adenopathy is unilateral unless the lesion has invaded the floor of the mouth in the anterior midline. In 275 cases studied by Taylor and Nathanson, 178 (65 per cent) developed a metastasis. This is usually a submaxillary node which is attached to the mandible and forms a single block with the primary lesion. Lymph nodes of the anterior jugular chain are most often invaded secondarily. Rarely a node of the subclavicular group may be invaded without previous submaxillary implants but when this occurs the node is usually situated posteriorly.

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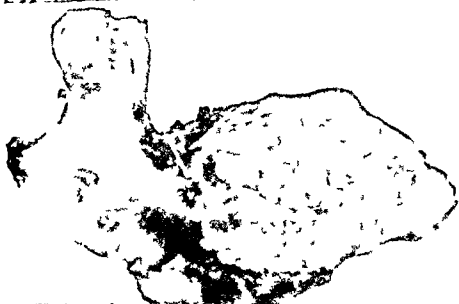
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Death usually occurs in unsuccessfully treated cases or in post-treatment recurrences and is usually caused by complications such as hemorrhage and bronchopneumonia. Distant metastases, although sometimes found, are seldom directly responsible for the death.

# Diagnosis

**Clinical Examination**—The examination of a carcinoma of the lower gingiva should not be limited to mere inspection but should always be completed by careful palpation of the floor of the mouth, the gingivobuccal gutter, the soft palate and the soft tissues of the cheek. In general the diagnosis of the primary lesion will offer no difficulties, but the clinical impression should always be substantiated by a biopsy. The careful inspection and palpation

FIG. 1



9 10 11 12 13 14 15 16 17 18

FIG. 1

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

should establish as far as possible the extent of the tumor and consequently will be of capital importance in the therapeutic decisions.

**Roentgenographic Examination**—A roentgenogram of the mandible is an absolute requisite in all cases of carcinoma of the gingiva, for it may reveal evidence of bone invasion even when this is not clinically suspected (Figs 213 and 217). On the other hand, lack of radiographic evidence of bone invasion is not an absolute certainty of its absence. Also it is frequent that in surgical specimens the carcinomatous infiltration is found to extend far beyond the radiographic evidence of such extension.



Fig. 217—Roentgenogram of same patient illustrated in Fig. 215 showing diffuse involvement of the bone.

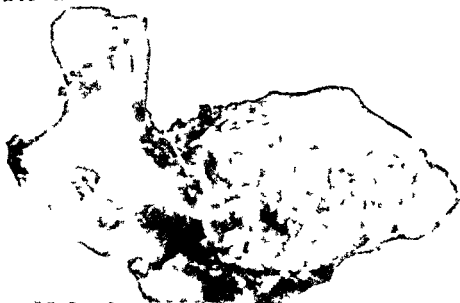
**Differential Diagnosis**—Chronic inflammatory ulcerations of the gingiva, which are sometimes observed in the neighborhood of defective teeth, may sometimes be taken for early carcinomatous lesions. Such inflammatory ulcerations will rapidly disappear after extraction of carious teeth and improvement of the oral hygiene. If there is outgrowth in addition to the ulceration, a biopsy should be done at the time of extraction. Chronic inflammatory outgrowths of the gingival mucous membrane are smooth, tongue-like projections found between the teeth. They may bleed easily when traumatized, but they are not accompanied by ulceration.

Peripheral giant-cell tumors are commonly observed on the gingiva, more often in the premolar area, but also in the area of the gross molars. They are

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1 21



9 10 11 12 1 13 14 15 16 17 18

Fig. 1

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100



**SURGERY**—A local excision of a carcinoma of the gingiva through the mouth aims to conserve part of the horizontal branch of the mandible and to maintain continuity of the mandibular arch. Such an operation is only justified in early cases where the tumor is limited to the alveolar ridge of the mandible. Under these circumstances, however, roentgentherapy is just as successful. Such economical resections are consequently not justified unless competent roentgentherapy is not available or unless it is a case of a very differentiated epidermoid carcinoma which does not respond well or which may be difficult to sterilize by means of radiations.

In the treatment of lesions which have already invaded the surrounding structures, which present bone invasion or lymph node metastases, the only curative form of treatment is a radical resection of the mandible and of the submaxillary and cervical lymph nodes. This radical operation includes not only a resection of the entire half of the mandible, but a neck dissection as well. Some authors believe that a partial upper neck dissection is sufficiently extensive unless upper cervical metastases are already palpable. This radical operation, however, has been accompanied in the past by a rather high operative mortality. Taylor and Nathanson collected forty-one cases of jaw resections for carcinoma of the lower gingiva in which there had been five operative deaths. These deaths were due to hemorrhage, pulmonary embolus, septicemia, and bronchopneumonia. Recent progress in anesthesia, control of shock, and postoperative infections has contributed a decrease of this operative mortality. At any rate, such a radical operation should only be contemplated in the treatment of these tumors when they have invaded adjacent structures or extended to the lymph nodes.

The cosmetic result following this mutilating operation is quite satisfactory unless the skin is invaded and has to be resected (Fig. 219). If the mandible is divided close to, but not beyond the midline, there is seldom a deviation of its normal position and patients are able to masticate food without difficulty. A complete resection of one-half of the bone is preferable to its division at the level of the angle of the mandible. If the vertical portion of the bone is allowed to remain, while accomplishing no purpose, it will be quite bothersome and recurrences often develop on the stump. If the operation does not require excision of large portions of the skin, the facial defect is not usually very marked, and the bone defect with the accompanying depression of the face is usually well dissimulated. Attempts to repair the mandibular defect by means of rib grafts have seldom been successful because of usual secondary infection. Specially fitting dentures, sometimes hinged to an upper plate, may be satisfactorily adapted.

**Prophylactic Neck Dissection**—Obviously when a radical resection of the mandible is to be done, it should always be accompanied by at least an upper neck dissection, whether nodes are palpable or not. On the other hand, when a conservative form of treatment is decided upon for early lesions in which no metastatic nodes are palpable, there is the question of treating possible metastatic lymph nodes. About 30 per cent of all patients without a metastasis when first examined will develop an adenopathy later (Taylor and Nathanson), but this is an over-all figure which includes all cases. In general,

smooth, shiny tumefactions with areas of induration and others of considerable softness. Their clinical appearance is typical, and biopsy will rapidly substantiate the clinical impression. In children, the clinical diagnosis will have the added support of the fact that carcinomas of the lower gingiva are practically never seen in juveniles. When these lesions have received an injury such as incision or extraction of teeth, they may become ulcerated and secondarily infected. When secondary infection takes place, central necrosis pain, and even trismus may contribute to give them the appearance of a malignant tumor. These giant cell tumors develop slowly and recur following incomplete excisions. Some rare inflammatory lesions of the mandible may show a fibrous structure and appear pedunculated, becoming ulcerated only after trauma.

Leucoplakia of the lower gingiva is sometimes observed in edentulous patients. These patches of leucoplakia may give rise to a carcinoma in that area and, for this reason, should be closely watched for indications of biopsy.

Primary benign and malignant tumors of the lower jaw as well as metastatic lesions to this bone may become ulcerated in the mouth and appear rarely as a primary carcinoma of the lower gingiva. When this takes place, the biopsy will make the differential diagnosis for it usually will reveal evidence of a type of tumor (adenocarcinoma, ameloblastoma, etc.) very different from the epidermoid carcinomas which are usually found in this region.

### Treatment

**ROENTGENTHERAPY**—External and peroral roentgentherapy have been successful in eradicating early primary tumors of the lower gingiva, even when there was some evidence of bone invasion. The advantage of this form of treatment lies in the protraction of therapy over a period of several weeks and thus avoiding excessive changes in the bone. In general, however, this conservative form of therapy is only justified in early lesions limited to the gingiva and without evidence of submaxillary metastases. If this form of treatment fails, a radical operation can be performed with as good a chance of success provided the roentgentherapy has been applied in a protracted manner with the use of well filtered high voltage radiations through as small fields as possible.

**CURIETHERAPY**—*Surface curietherapy* with specially molded applicators has given successful results, but, in general this form of treatment is followed by a high incidence of complications. Limited necrosis of the mandible in particular can be avoided by a protracted application of roentgentherapy. *Interstitial curietherapy* should not be considered in the treatment of these tumors because in addition to the usual disadvantage of such a procedure there may also be bone necrosis and sequestration.

At any rate any form of radium treatment can only be justified in small lesions in which there is no evidence of metastases. It is doubtful whether, if limited to this group, the application of curietherapy would have any advantage over an equally skillful application of external and peroral roentgentherapy.

the cases chosen for a conservative form of treatment are early usually differentiated tumors which will have a small chance of developing metastases, and for this reason a prophylactic neck dissection may not be justified. In addition, if there is a recurrence of the primary lesion after such conservative treatment, with or without an adenopathy, the proper means of approach will be a radical surgical excision.

### Prognosis

With an adequate therapeutic approach, the prognosis of carcinoma of the lower gingiva is a rather good one. In a series of fifty-seven patients with carcinoma of the lower gingiva, Martin reported fifteen (26 per cent) surviving five years after treatment. In Martin's series, none of the patients who presented a metastasis on admission survived five years. This is perhaps a consequence of too conservative an approach. Melville reported the results obtained in carcinoma of the lower gingiva together with those of the floor of the mouth treated by surface application of radium molds, of sixty-nine patients, thirty-one (45 per cent) were well three years after treatment. In a group of fifty-five patients with carcinoma of the lower gingiva and of the buccal mucosa who were treated by radical resection by Ellis Fischel, thirteen (24 per cent) were well at the end of five years (Keyes).

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## TUMORS OF THE HARD PALATE

### Anatomy

The hard palate is a U-shaped area, limited anteriorly and laterally by the upper dental arch, which forms the roof of the mouth. The anterior two thirds of the hard palate are formed by the palatine process of the superior maxilla. Its posterior third is formed by the horizontal portion of the palatine

Fig 218



Fig 219

Fig 218—Epidermoid carcinoma of the lower gingiva with extensive invasion of the skin of the cheek and chin

Fig 219—Same patient after wide surgical excision of the mandible and soft tissue of the cheek and chin. The resulting defect may be attenuated by plastic repair

### Incidence and Etiology

A large proportion of the tumors which develop on the hard palate are of the mucous and salivary gland type. They are variously referred to in the literature as mixed tumors, endotheliomas, embryomas, adenocarcinomas, fibromyxosarcomas and adenoid cystic tumors. It is now an accepted fact that these cells have an epithelial origin (Krompecher) and that the mucoid material, cartilage etc. is a product of metaplasia. These tumors arise from the mucous and minor salivary glands and although they may be found elsewhere in the oral cavity they are most frequently found on the hard palate. Of forty-two cases of mucous and salivary gland tumors of the oral cavity reported by Ahlborn sixteen were on the hard palate. Ten of these patients were women and six were men, and although they were found in a wide range of ages seven of the sixteen occurred between 50 and 60 years of age. These tumors have a similarity to others which arise from the major salivary glands, the lacrimal glands and the trachea.

Epidermoid carcinomas of the hard palate are very rare. In a series of about 5,000 cases of cancer of the oral cavity observed from 1907 to 1938 by New (1941) there were only twenty-five cases of epidermoid carcinoma of the hard palate. There is only one epidermoid carcinoma for every three or four mucous and salivary gland tumors of the hard palate, and unlike these the carcinomas are seldom observed in females.

Occasional trauma and the use of dental plates have been held as possible causes of cancer of the hard palate. In many instances difficulty with a dental appliance is a consequence rather than the cause of the tumor.

In Vizagapatnam, India Kim and Subra-Rao found fifty-two carcinomas of the palate among 335 cases of carcinoma of the oral cavity. This high incidence has been considered as due to nutrition from the habit of smoking a local type of cigar (*chutta*) a poor substitute for tobacco. The lighted end reportedly goes out and the smokers resort to *Addi Poga* or reverse smoking, putting the lighted end inside the mouth. Large areas of leucoplakia usually precede the development of carcinoma.

### Pathology

**Gross Pathology**—Mucous and salivary gland tumors develop on the posterior half of the hard palate on one side of the midline (Fig. 221). In general they are well encapsulated and have a polylobated surface. They may extend to the adjacent area of the soft palate and grow through it to the nasopharynx. Without showing any tendency to ulceration of the mucous membrane they may erode into the maxillary bone and erupt into the floor of the nasal fossa or the maxillary antrum. On section they contain hyalinized connective tissue which forms septa. Cartilage may also be present.

Epidermoid carcinomas of the hard palate are usually superficially ulcerated and rarely localized. The ulceration may extend beyond the midline and invade secondarily the upper gingiva or the soft palate and later the bone.

bone In the midline of the hard palate there is a linear raphe The mucous membrane is a stratified squamous epithelium which appears corrugated and pale in color on the anterior third of the roof of the mouth but is smooth and darker on the posterior two thirds The bone is covered by dense tissues formed by the periosteum and mucous membrane which are intimately adherent on the anterior half The palatine glands, a group of some 250 independent though closely packed glandular aggregates, lie between the mucous membrane and the periosteum (Fig 220) on the posterior half of the hard palate (Orban) These racemose glands, producing mostly mucus, are continuous with those found near the anterior surface of the soft palate (about 100 in number) and those found in the uvula (about twelve)

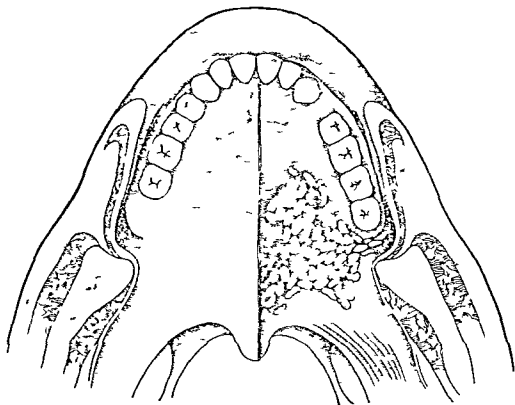


Fig 220—Inferior view of the hard palate showing mucosal rugae on the anterior half and racemose glands lying beneath the epithelium on the posterior half

**Lymphatics**—According to Rouviere the network of lymphatics of the hard palate runs posteriorly to a point behind the dental arch from where it diverges in three directions (1) to the deep lymph nodes of the neck, (2) to the lymph nodes of the submaxillary region and (3) to the retropharyngeal lymph nodes Of these only the first is constantly present The lymphatic vessels traveling to the deep nodes of the neck pass under the mucous membrane of the retromolar space, descend along the anterior border of the vertical branch of the mandible pass inside of the submaxillary gland and end in the deep nodes of the subgastric group on the anterior jugular chain The lymphatics of the roof of the mouth may be crossed in the midline and end on the corresponding nodes of the opposite side

ever, the perforation is sharply outlined, while in the malignant group the perforation through the bone may be quite diffuse

**Biopsy**—There has been no claim that a benign or malignant tumor of the salivary gland type has shown any faster growth following a biopsy. However, in the presence of a clinically established diagnosis of mucous and salivary gland tumor, a biopsy should be performed only when it is certain to be followed by a wide excision. A biopsy to be of any value, has to break through the capsule of the tumor and consequently will result in earlier ulceration and more discomfort. In the aged individual, abstention might be more beneficial to the patient and be merely of academic interest medically. An aspiration biopsy may be successfully done. The biopsy of ulcerated lesions of course, can be carried out without danger. Superficial biopsies of the salivary gland tumors may not show tumor when they are not taken deep enough.



Fig. 223—Fibrosarcoma of the superior maxilla with invasion and ulceration of the hard palate

**Differential Diagnosis**—In general the clinical examination alone will be sufficient to establish a diagnosis of mucous or salivary gland tumor in spite of their intricate histologic structure. They can easily be differentiated from *papillomas* of the hard palate which occur more often and have a typical papillary, nonulcerated appearance. A benign exostosis of the bones of the palate, which occurs usually in the anterior midline, is called *torus palatinus*. The fact

**METASTATIC SPREAD**—Only the malignant group of mucous and salivary gland tumors metastasize, and then only after long years of development. They seem to have a tendency to produce distant blood borne metastatic rather than lymphatic spread.

Only one fourth to one third of the epidermoid carcinomas of the hard palate develop metastases, usually found to be in the upper cervical or submaxillary regions. Distant metastases are seldom observed.

**Microscopic Pathology**—The term mixed tumor which is often given to the mucous and salivary gland tumors is employed to describe their complex nature rather than to imply a complex origin (Stewart). Some of these tumors, however, particularly those with malignant features, have comparatively simple structures which do not resemble the classical mixed tumors. Broders groups them under the single heading "adenocarcinomas of the mixed tumor type." Stewart reserves the label of adenocarcinomas for the malignant group, recognizing that the transition from benign to malignant is a very gradual one. It is impossible histopathologically to establish a definite division between the benign and the malignant. Actually, the only sure criterion of malignancy is the production of metastases, which usually occur late. Reuter will, following an earlier classification by Masson, classify the mucous and salivary gland tumors into three groups: (1) benign, (2) semimalignant, and (3) malignant. The classification is not a purely histologic one for it takes into consideration clinical observations. Under this classification, tumors are considered as *malignant* when they produce metastases or when they show infiltrative and destructive properties without tendency toward encapsulation. The *semimalignant* tumors have a capsule but are very cellular, with the cells showing an atypical and polymorphous, hyperchromatic or polymorphous nuclei with numerous mitoses. The intercellular substance may be quite sparse and the capsule may present infiltration by tumor cells or there may be nodules outside of it. All tumors which are well encapsulated, do not give metastases, and show none of the previously described elements of the semimalignant group are called *benign*.

Of these three groups of tumors, the mixed tumor predominates. It is usually fibroepithelial but myxomatous tissue and cartilage may also be present. The papillary cystadenoma which is usually classified as semimalignant is seldom observed. The highly differentiated type is encapsulated or shows cylindromatous areas or mucus producing glandlike structures. In very undifferentiated tumors there may be some epidermoidlike structure.

The malignant tumors offer the greatest difficulty with regard to classification because of their varied structures. When mixed tumor characteristics are present with myxomatous and cartilaginous tissue, the diagnosis is simplified. When epithelial tissue is lacking, however, the tumor may have a sarcomatous appearance. Only by a thorough search will clusters of epithelial cells be discovered. The adenocarcinoma contains mucin in the glandlike structures. The cells may be arranged in strands, alveoli or tubular forms. These tumors may, however, present a structure very similar to that of the adenoid cystic



that this occurs in the midline and on the anterior third of the hard palate should be enough to establish the diagnosis. *Syphilitic gumma* of the hard palate is very rare. In the presence of ulceration and secondary infection it may be difficult to differentiate this syphilitic lesion from an epidermoid carcinoma. The biopsy, however, will show only chronic inflammation and the lesion will rapidly disappear under antisymphilitic treatment. *Dentigerous cysts* and *ameloblastomas* of the upper jaw may grow slowly in the form of a non-ulcerated, smooth tumefaction which may be confused with salivary and mucous gland tumors. These tumors of the jaw, however, usually arise in the region of the upper alveolar ridge. The same may be true of a carcinoma of the antrum. It should be noted that the same type of mucous and salivary gland tumor may arise from the maxilloethmoidal region and that in their development they may secondarily extend to the palate. A differential diagnosis with the rare sarcomas of the maxilla (Fig 223) may be difficult upon inspection, but the presence of pain and ulceration and the rapidity of growth may help distinguish them. The biopsy will be conclusive in most instances.

### Treatment

**SURGERY**—Salivary and mucous gland tumors, whether benign or malignant, require surgical excision in the young patient. In the early benign group, the excision will be rather simple because of the usual encapsulation of the tumor. In the more advanced cases with bone perforation, the difficulties in excision, the extent of the defect, and the chances of local recurrence are considerably greater. In aged individuals, however, depending on the growth rate of the tumor, abstention is probably well justified.

Sometimes a subperiosteal excision of a benign tumor can be performed without touching the integrity of the bone. Very often, however, the salivary gland tumor is not detachable from the bone without breaking its capsule, and the excision implies the necessity of extirpation of part of the hard palate. This results in a permanent opening into the antrum and nasal fossa (Fig 227). The resulting defect will be well worth the elimination of the chance of recurrence. This defect may be easily alleviated by the use of a prosthesis (Ackerman). In very extensive tumors which have involved the infrastructure of the superior maxilla and nasal fossa, a radical excision implies a major defect. Electrosurgery is still favored for this large type of resection (Ohlgren). But in general, the success of any type of technique depends greatly on skillful performance. Epidermoid carcinomas of the mucous membrane of the hard palate which are well delimited should also be treated surgically. A radical neck dissection is the treatment of choice for metastatic adenopathy of the neck.

**RADIOTHERAPY**—Mucous and salivary gland tumors develop slowly as a rule and do not present a large amount of cellular mitoses. Theoretically they should not be radiosensitive, and, in fact, they are only slightly so, although they are more affected by radiations as they are more malignant. Ahlborn reported that in some cases the tumor shows definite radiosensitivity. How



Fig 24—Hypertrophy and hyperplasia of palatine glands suggesting tumor (Courtesy of Dr Hamilton Robinson Professor of Oral Pathology Ohio State Dental College Columbus Ohio)



Fig 25—Torus palatinus (Courtesy of Dr Hamilton Robinson Professor of Oral Pathology Ohio State Dental College Columbus Ohio)

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## TUMORS OF THE LOWER JAW

## Anatomy

In the adult, the lower jaw or mandible is a single bone with a symphysis in the midline. It is usually divided into a *corpus* and two ascending branches. The *corpus* is horseshoe shaped and is formed by two lateral branches. The superior borders of these branches form the alveolar ridge and lodge the teeth. The ascending branches of the mandible are roughly rectangular, their internal surfaces contain the orifice of entrance of the dental nerve and artery. The posterior borders of the ascending branches end in the condyle.

The mandible is formed mostly by spongy bone entirely surrounded by remarkably dense bone. Each half of the mandible contains a long canal running horizontally along the dental roots, this canal is occupied by the dental nerve and vessels.

The teeth and their immediate supporting structures have a complex origin. At about the sixth week of intrauterine life, the oral epithelium proliferates in twenty places to form the anlagen for the ten maxillary and ten mandibular deciduous teeth. From these primordia, the enamel organs of the deciduous teeth differentiate and the same epithelial proliferations contribute the anlagen for the thirty-two permanent teeth. Each tooth bud undergoes a complex differentiation until enamel organs evolve. Each enamel organ consists of an outer squamous epithelial layer, an inner columnar epithelial layer (ameloblasts), a central core of stellate reticulum, and a less differentiated stratum intermedium. The enamel organ lays down the enamel and also, by

ever, radiosensitivity does not imply radiocurability. Actually, when these tumors are treated by radiotherapy alone, they do show a slow and delayed response but are seldom completely sterilized. On the basis of this, the value of preoperative and postoperative irradiation is very questionable.

Radiotherapy in the form of external roentgentherapy as well as specially fitting radium molds may be applied to epidermoid carcinomas of the hard palate which have already extended beyond the midline and are consequently not resectable. Very little experience has been accumulated in the treatment of these uncommon epidermoid carcinomas but their treatment by radiation therapy when resection is impossible, is well justified.

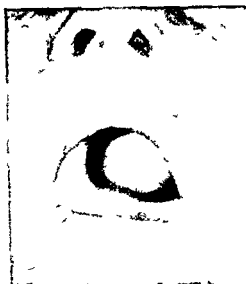


Fig. 226



Fig. 227

Fig. 226—Typical smooth unilateral hemispherical mucous and salivary gland type of tumor of the hard palate.

Fig. 227—Same patient after surgical excision of the tumor. The resulting defect communicating with the nasal fossa was easily occluded by a prosthesis.

### Prognosis

The prognosis of the benign mucous and salivary gland tumors is a very good one. It is difficult to give an estimate of the prognosis of the malignant group because the material reported is not usually comparable. In a series of sixty patients with salivary gland tumors of the hard and soft palate, benign and malignant, surgically treated by New (1941), twenty (33 per cent) were reported as living five years or longer after treatment. Martin reported on a group of fifteen patients with malignant salivary gland tumors of the hard and soft palate, of which six (40 per cent) were well and without symptoms five years after surgical treatment.

The prognosis of epidermoid carcinomas of the hard palate is not as good as that of salivary gland tumors in general. In the verrucous type of carcinoma, however, which seldom metastasizes, a wide excision will often be followed by a definite cure.

or solid ameloblastoma shows epithelial proliferation in a connective tissue stroma of mesenchymal type of cells. The epithelium is arranged in cords, strands, or follicles strikingly similar to the arrangement of the epithelium in dental buds, dental laminae or enamel organs (Fig 231). The differentiation of these dental anlage like structures continues up to the point where function (laying down of enamel) begins. The cells of an ameloblastoma do not assume this function, degeneration begins instead at the expense of the central stellate cells of the enamel organs homologues. This retrogression leads to the formation of a multicystic tumor. The tall columnar cells of the solid ameloblastoma may be compressed to cuboidal or squamous forms (Fig 232) and the stellate central cells are replaced by mucoid fluid. Any transitional stage between these two extremes, solid or cystic, may be observed but careful examination reveals the arrangement of cells in the form of odontogenic tissues in some areas (Robinson).

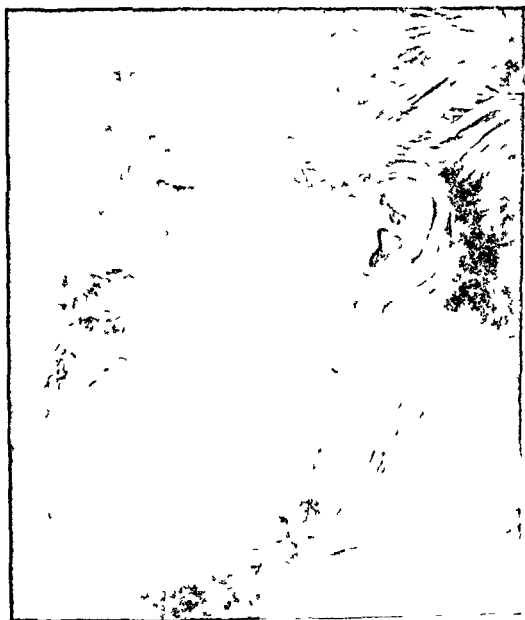


Fig 228—Huge ameloblastoma of the mandible which developed without interference for thirty-five years

*Ewing's sarcomas* arise from within the marrow cavity and thicken the cortical bone, and then tumor cells gradually permeate by way of the haversian canals through the cortex to elevate the periosteum. The cellular appearance is similar to that observed in other bones (see Tumors of the Bone).

*Osteogenic sarcomas* occur more frequently in the lower than in the upper jaw. Stout reported that in a series of sixteen osteogenic sarcomas of the jaw,

proliferation of its apical end, forms a tube of epithelium, the sheath of Hertwig which outlines the future tooth root. Within the hollow of the enamel organ, the mesenchymal tissue differentiates into the dental papillae which contribute the dentin and pulp. The mesodermal tissues surrounding the developing tooth contribute the cementum of the tooth, the periodontal membrane and the alveolar and supporting bone. During this process, epithelial rests may be left behind from the sheath of Hertwig and from the dental lamina which connects the oral mucosa to the young enamel organ (Robinson).

### Incidence

There are relatively few tumors of the lower jaw compared with tumors of other oral structures. In general tumors of the mandible occur in young individuals. Some of the slowly growing tumors may be found in older people, but, as a rule the onset of tumor growth has taken place earlier. Fibrosarcomas and giant cell tumors develop most commonly in adolescents in their second or third decade of life. According to Robinson, 70 per cent of the ameloblastomas are found in patients 10 to 35 years of age. Ewing's sarcomas are generally found in patients under 20 years of age. Osteogenic sarcomas may be found in individuals of all ages but they are not infrequent in young persons.

### Pathology

**Gross and Microscopic Pathology**—A few tumors of the lower jaw warrant detailed description.

The *fibrosarcoma* of the mandible is usually multilocular or diffuse, involving the corpus. On section the tumor shows a variable resistance according to its cellularity. Microscopically it exhibits a great difference in connective tissue maturation. Connective tissue is interlaced with bone spicules, and the tumor varies from the very cellular to churning (Billings).

*Giant cell tumors* of the lower jaw may be peripheral or central. The peripheral giant cell tumor may, however, grow to involve the body of the mandible and become indistinguishable from the central lesion. These tumors displace the mandible laterally, displacing and separating the molars and premolars. They rarely become ulcerated, but after extraction of teeth a granulating growth is usually present and a necrotic ulceration may also result. Giant cell tumors may extend to involve most of the mandible. Their microscopic appearance is typical (see Tumors of the Bone page 972). It is a debatable question whether these tumors ever become malignant (Stout).

The *ameloblastoma* is an epithelial tumor derived from cells which have a potentiality for enamel formation. This tumor is more commonly found in the mandible (85 per cent) than in the upper jaw. It forms a cystic mass within the body of the mandible and often reveals surface lobulations. On section, the consistency is usually firm, but it may be cystic with fibrous trabeculae or occasional bone spicules. The tumor is sometimes found in some transitional phase between solid and cystic forms (Robinson). Microscopically, the young

or solid ameloblastoma shows epithelial proliferation in a connective tissue stroma of mesenchymal type of cells. The epithelium is arranged in cords, strands or follicles strikingly similar to the arrangement of the epithelium in dental buds, dental laminae or enamel organs (Fig. 231). The differentiation of these dental anlage like structures continues up to the point where function (laying down of enamel) begins. The cells of an ameloblastoma do not assume this function; degeneration begins instead at the expense of the central stellate cells or the enamel organs homologues. This retrogression leads to the formation of a multicystic tumor. The tall columnar cells of the solid ameloblastoma may be compressed to cuboidal or squamous forms (Fig. 232) and the stellate central cells are replaced by mucoid fluid. Any transitional stage between these two extremes, solid or cystic, may be observed, but careful examination reveals the arrangement of cells in the form of odontogenic tissues in some areas (Robinson).

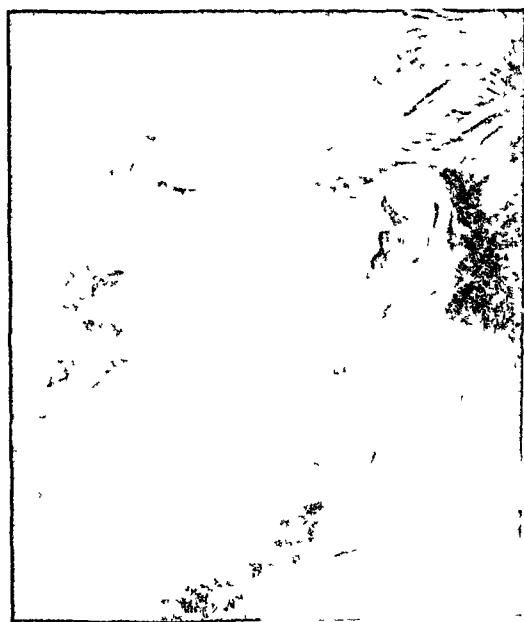


Fig. 228—Huge ameloblastoma of the mandible, which developed without interference for thirty-five years.

*Ewing's sarcomas* arise from within the marrow cavity and thicken the cortical bone, and then tumor cells gradually permeate by way of the haversian canals through the cortex to elevate the periosteum. The cellular appearance is similar to that observed in other bones (see Tumors of the Bone).

*Osteogenic sarcomas* occur more frequently in the lower than in the upper jaw. Stout reported that in a series of sixteen osteogenic sarcomas of the jaw,



Fig 229—Roentgenogram of a surgical specimen showing an ameloblastoma of the mandible with typical cystic areas and trabeculations.

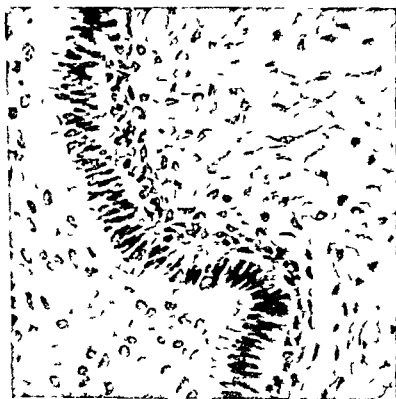


Fig 230—Photomicrograph of a solid ameloblastoma. From left to right mesenchymal cell stroma, ameloblast like cells, stratum intermedium like layer and stellate cells can be seen mimicking normal enamel organ. (Courtesy of Dr. Hamilton Robinson, Professor of Oral Pathology, Ohio State Dental College, Columbus, Ohio.)



twelve occurred in the mandible. They may present all the variants which are characteristic of this form of tumor. They may arise on the basis of a pre-existing Paget's disease or rarely osteitis fibrosa cystica. In general, they grow rapidly and may become ulcerated within the mouth.



Fig. 221—Photomicrograph of a solid ameloblastoma showing enamel organlike follicles, small tooth budlike follicles, and dentin lamina-like strands. (Courtesy of Dr. Hamilton Robinson, Professor of Oral Pathology, Ohio State Dental College, Columbus, Ohio.)



Fig. 232—Histologic appearance of an ameloblastoma showing focal areas of keratinization.

**METASTATIC SPREAD**—Fibro-osteomas and giant cell tumors do not metastasize. Ameloblastomas metastasize very rarely (Schweitzer). Ewing's sarcoma quite characteristically metastasizes to other bones, to the regional lymph nodes and to the lungs. Osteogenic sarcomas metastasize with preference to the lungs but not to regional nodes.



Fig 220—Roentgenogram of a surgical specimen showing an ameloblastoma of the mandible with typical cystic areas and trabeculations

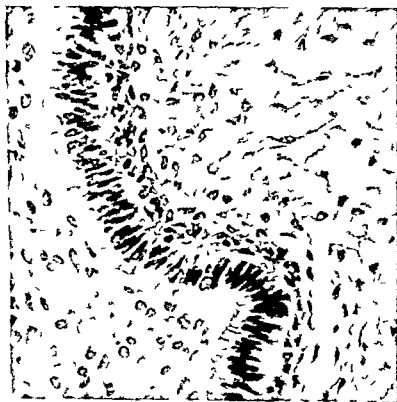


Fig 230—Photomicrograph of a solid ameloblastoma. From left to right mesenchymal cell stroma, ameloblast like cells, stratum intermedium like layer and stellate cells can be seen mimicking normal enamel organ. (Courtesy of Dr. Hamilton Robinson, Professor of Oral Pathology, Ohio State Dental College, Columbus, Ohio.)

### Diagnosis

The diagnosis of tumors of the mandible may be very difficult. Slow evolution and lack of symptoms generally designate a fibro-osteoma, giant cell tumor, or ameloblastoma. Rapidity of growth and pain in a young individual points to a diagnosis of Ewing's sarcoma or osteogenic sarcoma.

The roentgenographic examination of the mandible contributes valuable additional information to the physical findings, but it is rarely diagnostic in itself. A cystic loculated appearance is sometimes characteristic of ameloblastomas (Fig 229) but giant cell tumors, metastatic carcinomas, and various types of cysts may also mimic this image (Fig 234). Bone spicules growing at right angles to the surface of the mandible may be found in Ewing's sarcoma, and they may also be seen in osteogenic sarcomas.

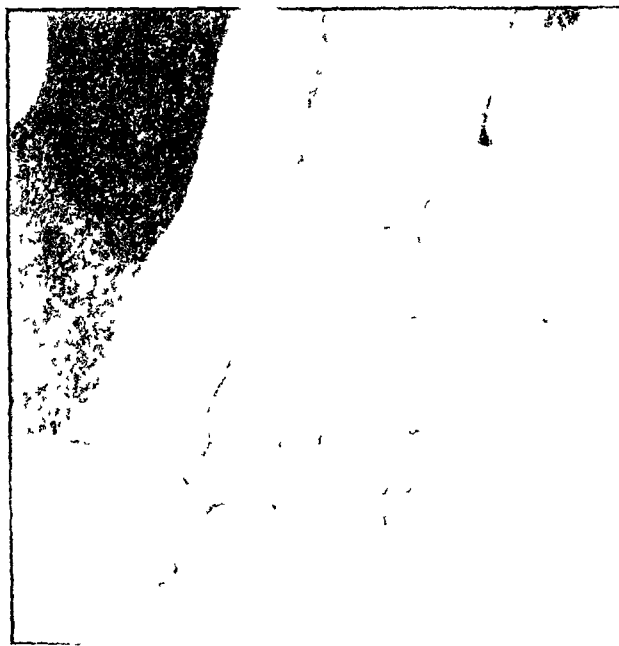


Fig. 234—Metastatic osteogenic sarcoma of the mandible in a 12 year old boy. The primary lesion arose from the femur. (Courtesy of Dr. Hamilton Robinson, Professor of Oral Pathology, Ohio State Dental College, Columbus, Ohio.)

**Differential Diagnosis**—There is usually no difficulty in the diagnosis of fibro-osteoma, for the clinical history and roentgenologic findings are typical. The giant cell tumors have to be differentiated from all other lesions which cause a cystic area within the mandible. Ameloblastomas may cause considerable difficulty, for they also have to be differentiated from various cystic lesions. We have seen two instances of suspected ameloblastoma in which the mandible was invaded secondarily—first, by a mixed tumor of the submaxil-

### Clinical Evolution

The *fibro osteoma* usually appears at the age of puberty. As the tumor gradually increases in size, it causes no pain, and any symptoms which develop are due to the mechanical difficulties induced by deformity and swelling.

*Giant cell tumors* develop slowly and may reach a huge size (Fig 233). They usually appear as nonulcerated tumefactions of the outer aspect of the mandible, or they may enlarge the width of the alveolar ridge. The teeth become separated and displaced. When teeth are extracted, a granulating easily bleeding tissue may appear in the socket. Pain is seldom present unless secondary infection has taken place. The general condition of the patient is affected if the tumor interferes with eating or if there is marked bleeding or infection.



Fig 233—Roentgenogram of a huge giant cell tumor of the mandible which had recurred several times after inadequate excisions.

In *ameloblastomas* the slow progress of the tumor rarely produces any symptoms. Occasionally, however, they cause numbness in the region of the intramandibular nerve or a toothache. Over a period of years, the tumor may attain a large size and become visible (Fig 228). Fractures of the bone may be a complication of these tumors. Secondary infection occurs at times through the mouth. These tumors distend but do not infiltrate the surrounding soft tissues. They rarely cause death.

*Kiuping's sarcomas* develop faster than the preceding tumors. Pain accompanies their growth becoming progressively intense. The mass may rapidly involve both sides of the mandible. Both local and distant metastases are frequently found.

*Osteogenic sarcoma* of the mandible is invariably accompanied by severe pain and sometimes fever. A history of loosening of the teeth is usually given. The evolution of the tumor is rapid with equally rapid deterioration of the general condition. Distant metastases are the rule.

*Periodontal cysts* are closed epithelium-lined sacs formed in the periodontal membrane and adjacent structures usually at the periapex of a tooth. Their incidence is difficult to determine for they are often asymptomatic and discovered only by routine dental roentgenographic examination. They are more common in the maxilla (63 per cent) than in the mandible (37 per cent) and prevail in the anterior regions of the jaws. They are two and one-half times more numerous on pulpless teeth than on teeth with vital pulps (Stafne). The epithelium of these cysts is derived from periodontal epithelial debris. The periodontal cyst is usually preceded by a dental granuloma on a pulpless tooth; McCrea showed that all of the dental granulomas contain proliferating or resting epithelium. The epithelium is stimulated to proliferate by the inflammatory or reparative process.

Three main types of periodontal cysts occur, the radicular or periapical type at the apex of the tooth root, the lateral type at the side of the tooth root, and the residual type which may be left after extraction of a tooth with incomplete removal of one of the other two types. Those cysts which arise laterally to the permanent tooth roots anterior to the first molar and which contain irregular calcified tooth elements may be variants of periodontal cysts arising at the root ends of deciduous teeth. The periodontal cysts are lined by stratified squamous epithelium within a connective tissue capsule. In rare instances, the lining epithelium may be columnar. They usually contain sterile fluid.

Roentgenographically, periodontal cysts appear as more or less elliptical, radiolucent areas with fairly well differentiated radiopaque borders. A tooth root is usually seen projecting to or into the radiolucent area (periapical type) but it may be alongside of a root (lateral type) or in a region formerly occupied by a root (residual type). They must be differentiated from dental granulomas, primordial cysts, dentigerous cysts, globulomaxillary cysts, neoplasms, and osteitis fibrosa cystica. They should be completely enucleated because on regrowth they appear to become more invasive and may in time become locally malignant. The prognosis is good if the cyst is removed completely.

lary gland and second, by a mixed tumor of the alveolar ridge. In each instance, the invaded mandible showed a cystic area. Rarely the very cellular fibro osteoma can be confused microscopically with osteogenic sarcoma. However, neoplastic osteoid will not be present, and the roentgenologic picture and clinical history are sufficient to differentiate. The formation of a tumor nodule outside of bone in which roentgenologically there is destruction of the mandible is almost certain evidence of an osteogenic sarcoma. In its undifferentiated state an osteogenic sarcoma may be difficult to differentiate from Ewing's sarcoma. The response to radiations alone often makes the diagnosis. Ewing's sarcoma, because of the fact that it suggests an infection, may be confused with osteomyelitis (see Tumors of the Bone, page 323).

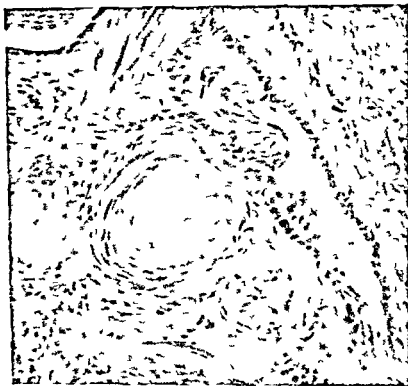


Fig. 27.—Photomicrograph of a periodontal cyst with epithelial whorls and a ductlike structure. This structure might proliferate to a new cyst or to a neoplastic growth (moderate enlargement). (Courtesy of Dr. Hamilton Pabin, Professor of Oral Pathology, Ohio State Dental College, Columbus, Ohio.)

Cysts of the jaw are very common lesions which enter into the differential diagnosis. Robinson divides these cysts of dental origin into periodontal, dentigerous and primordial (follicular) types in the following description.\*

The developmental cysts of the oral cavity are derived from ectodermal remnants. The sheath of Hertwig which outlined the developing roots, the dental lamina which connected the tooth bud and oral epithelium or enamel organs may be the sources of these remnants as well as inclusions at points of fusion of the primordia of the face and jaws.

\*Dr. Hamilton Pabin, Department of Oral Pathology, School of Dentistry, Ohio State University.



PROLIFERATION



DIFFERENTIATION



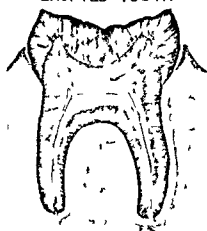
TISSUE FORMATION



TISSUE FORMATION



ERUPTED TOOTH



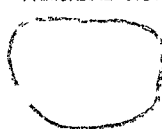
SOLID AMELOBLASTOMA



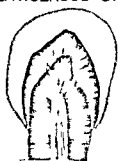
CYSTIC AMELOBLASTOMA



PRIMORDIAL CYST



DENTIGEROUS CYST



PERIODONTAL CYST



THE AMELOBLASTOMA IS AN EPITHELIAL NEOPLASM WHICH RESEMBLES DENTAL LAMINAE AND ENAMEL ORGANS UNTIL THE PERIOD OF AMELOGENESIS. IT MAY BE DERIVED FROM CELLS OF THE ORAL EPITHELIUM WITH A TENDENCY TO ODONTOGENESIS FROM REMNANTS OF THE SHEATH OF HERTWIG OR THE DENTAL LAMINA (EPITHELIAL RESTS) OR FROM ABERRANT TOOTH BUDS. IT BEGINS AS A SOLID TUMOR APING THE DENTAL ANLAGE AND ENAMEL ORGAN BUT NEVER FORMS ENAMEL. IT DEGENERATES AT THE EXPENSE OF THE STELLATE RETICULUM TO BECOME A MULTICYSTIC TUMOR.

THE PRIMORDIAL CYST IS A CYST OF THE JAW DERIVED FROM THE ENAMEL ORGAN IN ITS EARLY STAGES. BEFORE TISSUE FORMATION BEGINS THE STELLATE RETICULUM BREAKS DOWN AND FLUID COLLECTS BETWEEN THE INNER AND OUTER ENAMEL EPITHELIUM. THE CYST IS FORMED BY INTERNAL PRESSURE.

THE DENTIGEROUS CYST IS A CYST OF THE JAW CONTAINING THE CROWN OF A TOOTH. IT IS USUALLY DESCRIBED AS FORMED BY A BREAKDOWN OF THE STELLATE RETICULUM DURING AMELOGENESIS. THIS WOULD PRODUCE HYPOPLASTIC ENAMEL. IT APPEARS TO BE FORMED WITHIN THE REDUCED ENAMEL EPITHELIUM.

THE PERIODONTAL CYST IS A CYST FORMED IN THE PERIODONTAL MEMBRANE USUALLY AT THE ROOT END OF A PULPLESS INFECTED TOOTH. THE EPITHELIAL LINING IS DERIVED FROM THE EPITHELIAL RESTS (USUALLY REMNANTS OF THE SHEATH OF HERTWIG). THEY ARE COMMONLY THE SEQUELS OF DENTAL GRANULOMATA IN WHICH EITHER RESTING OR PROLIFERATING EPITHELIUM IS A CONSTANT FINDING.



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## CANCER OF THE NASOPHARYNX

## Anatomy

The nasopharynx or epipharynx is an open chamber situated just below the base of the skull and immediately behind the nasal fossa. It has an irregularly cubic form with six walls, two of which, the lateral walls, are symmetric. It is 4 cm in its transverse diameter, 4 cm in height, and 2 to 3 cm in anteroposterior diameter. The nasopharynx is the only one of the three portions of the pharynx which does not make up part of the digestive tract and which is incapable of obliteration.

The *anterior wall* is formed by the posterior nares or choanae, oval-shaped openings communicating with the nasal fossa and separated in the midline by the nasal septum. Through the choanae the nasopharynx is in close relationship with the posterior extremity of the second and third turbinates.

The *posterior wall* lies at the level of the first two cervical vertebrae and is sometimes almost continuous with the roof of the nasopharynx. Laterally, it extends to form the posterior limits of the fossa of Rosenmüller.

The *inferior wall* is a virtual one, formed by the soft palate, and extends from the posterior border of the palatine bones to the free border of the soft palate itself.

The *roof or upper wall* corresponds to the body of the occipital bone and to the adjacent part of the sphenoid. It is almost entirely made up of the lymphoid tissue which forms the pharyngeal tonsil or tonsil of Luschka. This lymphoid structure is divided in the midline by a deep fissure which extends anteroposteriorly and ends in a small depression, the pharyngeal bursa. The pharyngeal tonsil is relatively large in children but is atrophied in the adult.

strated. In large dangerous cysts, the entire tooth may be included in the tooth cavity and may be impossible to differentiate from larger periodontal cysts. The entire epithelium should be removed to eliminate the possibility of regression.

*Primordial cysts* are closed epithelial sacs formed by retrogression of the stellate pulp in enamel organs or tooth buds at any time before calcified tooth structures are deposited. They do not contain calcified structures and appear roentgenographically as more or less symmetrical radiolucencies with radiopaque borders. They may be single or multiple, unilocular or multilocular. Malap's primordial cysts sometimes occur as a familial disease ("erectusism"). The differential diagnosis must be made from neoplasms, residual cysts, epidermoid cysts and traumatic cysts. Multilocular primordial cysts may appear to be ameloblastomas roentgenographically. Careful clinical study is essential for the diagnosis of primordial cysts. The prognosis after the removal is excellent.

### Treatment

*Giant cell tumors* often recur after local excisions, they can be cured by wide resection, but this form of treatment is not justified for a benign tumor in young patients. Roentgenotherapy is used as treatment of choice (Laenhardt). The amount of radiation necessary is not considerable. It is preferable to administer small series of treatments at intervals of several months or even years. The regression of the tumor is slow and, because of this, the uninformed may consider them radioresistant. Isolated cases of ameloblastoma have been successfully treated with roentgenotherapy, however, this form of treatment has not yet proved itself superior over a wide resection (Kimm).

*Epitheliomas* are very radioresistant and have been successfully treated by radiation. No local surgical excision of these tumors and invariably in failure. Roentgenotherapy must be used to ensure a prolonged series of treatments is practicable in order to, facilitate resolution, without any adverse effects on the skin or mucous membranes. When roentgenotherapy fails it is most often due to the uncontrolled presence of distant metastases.

In *epitheliomas* the only true means of cure is radical resection with removal of the entire mandible, leaving the soft parts in place. Any other procedure will permit regrowth of the mandible in no matter how perfect manner it is replaced.

### Prognosis

The prognosis of the tumor is excellent. Giant cell tumor is also here a good prognosis, provided an adequate wide resection. Ameloblastomas have a somewhat poorer prognosis, but a good result is obtained if the tumor is completely removed. If amputation is not possible, and local recurrences may be expected in about 50 per cent of the cases. A complete regression is reported with Ewing's sarcoma of the mandible, but only by radical resection with removal of the entire mandible. The prognosis is poor. Parodontal cysts, epidermoid cysts, and keratin cysts have a good prognosis.

The posterior and lateral walls of the nasopharynx are surrounded by the pharyngeal fascia, which is strongly attached to the base of the skull just in front of the foramen magnum posteriorly and to the petrous portion of the temporal bone laterally. At the level of the eustachian tubes, this fascia is divided into a sort of gutter which is responsible for the strong attachment of



Fig. 237—Anatomic sketch of the bony structures of the base of the skull illustrating, 1, the position of the petrous portion of the temporal bone, 2, the foramen lacerum, and 3, the foramen ovale on the left side. This petrosphenoidal portion of the base of the skull provides easy access into the middle cerebral fossa.

the tubes to the base of the skull. The fascia thus forms an aponeurotic, fibrotic chamber entirely closed and very resistant which is continuous with the fibrous tissue occupying the foramen lacerum (Truffert). This conception is important for understanding the extension of tumors of the pharynx toward the middle cerebral fossa. The foramen lacerum

The *lateral walls* are the most important of all and they contain the pharyngeal orifice of the tubae auditivae (eustachian tubes). These openings are small, triangular, and infundibular in appearance. They are surrounded by a ridge, the *torus tubarius*, due to the salience of cartilage above and behind the opening, but not below or in front of it (Fig 236). Because of this salience of the cartilage of the eustachian tube a depression may be formed behind it which is called the *recessus pharyngeus* (fossa of Rosenmüller).



Fig 236—Posterolateral view of the nasopharynx showing 1 the choanae the posterior extremity of the second and third turbinates and the Eustachian tubes 2 Rosenmüller's fossa 3 the roof of the tonsil of Lu chka and 4 its very close relation with the sphenoidal sinus

The mucous membrane which covers the nasopharynx is formed by a stratified cylindrical and ciliated epithelium. This epithelium extends on the posterior wall and becomes squamous at the oropharynx. The same is true of the mucous membrane of the soft palate which is stratified cylindrical on its superior surface and it is covered by a squamous epithelium on its oral aspect. The transition occurs brusquely at its free border. Beneath the lining epithelium there are numerous closed lymphoid follicles in the corium. These lymphoid structures are particularly abundant on the rim of the eustachian tube (tonsil of Gerlach), but they are present on the lateral and posterior walls as well as on the nasopharyngeal surface of the soft palate where they contribute to form the upper arch of Waldeyer's ring.

foramen ovale constitute a zone of little resistance and an easy passway into the cranium (Fig 237). This "petrosphenoidal crossway" of Jacod (earlefour petrosphenoidal) is in close relationship to two very important anatomic structures—the gasserian ganglion and its branches and the cavernous sinus. The abducens nerve (VI) passes through the arcular cavity of the cavernous sinus and the oculomotor (III) and the trochlear (IV) are found in its lateral wall (Fig 239). The optic nerve (II) lies medial to the cavernous sinus.

**Relations**—The roof of the nasopharynx is in direct relation with the occipital bone, the sphenoidal sinus, and the cavernous sinus. The posterior wall is in relation to the first two cervical vertebrae through the medium of the pharyngeal fascia and the superior constrictor muscles. In front of the eustachian tube, the lateral wall of the pharynx is in relation with the maxillopharyngeal space, limited externally by the vertical ramus of the mandible. In this space is found the mandibular nerve descending from the foramen ovale. The lateral relationships of the eustachian tubes become unimportant by virtue of the strong attachment of the pharyngeal fascia. It must be noted that the facial and acoustic nerves (VII and VIII) are situated fairly high and are protected by the strong petrous portion of the temporal bone. Behind the eustachian tube, the fossa of Rosenmüller is in close relationship with the retroparotid space, which lies just behind and lateral to the nasopharynx. This space is limited anteriorly by the parotid gland and the styloid process and its muscles, posteriorly by the transverse process of the first cervical vertebrae, and laterally by the sternocleidomastoid muscle. This retroparotidian space contains the internal carotid, the internal jugular vein, and the glossopharyngeal, vagus, spinal accessory, and hypoglossal nerves (IX, X, XI, and XII), as well as the cervical sympathetic, as they emerge from the base of the skull (Fig 238). Lateral to these structures, three or four small lymph nodes may also be found.

**Lymphatics**—The lymphatics of the roof and of the posterior wall of the nasopharynx run anteroposteriorly and join in the midline. After passing through the pharyngeal fascia, they run to the right or left toward the retropharyngeal nodes. Some of the lymphatics, however, end in the highest nodes in the internal jugular and spinal chains on either side. The lymphatic vessels of the lateral wall of the pharynx are particularly rich at the level of the eustachian tube. They also follow an anteroposterior direction and may end in the retropharyngeal node or on the highest node of the jugular and spinal chains of the same side (Fig 238). Some of these deep cervical nodes of the jugular chain are very highly situated, and three or four of them may be found very near the emergence of the last cranial nerves.

### Incidence and Etiology

The incidence of cancer of the nasopharynx can only be estimated. In the past twenty years, the proportion of cases reported in the medical literature has increased due to better knowledge of this pathologic entity. Even today, many cases pass undiagnosed. In cancer centers, tumors of the nasopharynx are variously reported as making up between 0.5 and 1 per cent of all cases of cancer. Epidermoid carcinomas, lymphoepitheliomas, and lympho-

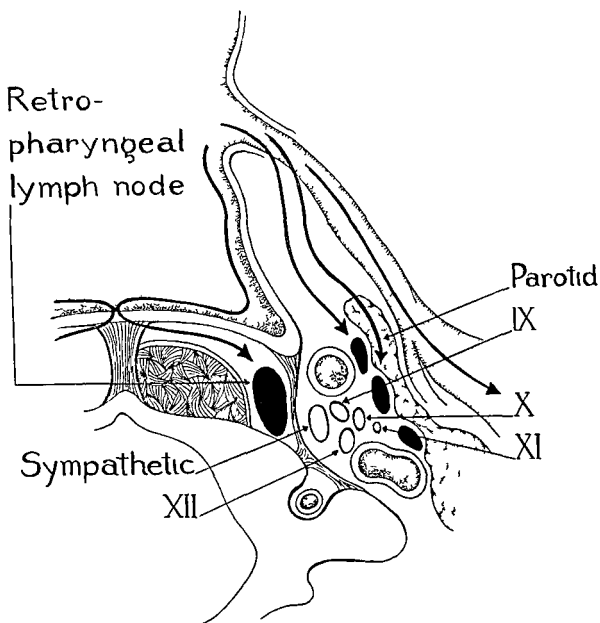


FIG 38—Schematic illustration of the lymphatics of the nasopharynx ending in the retropharyngeal lymph nodes or in the Krause group of nodes of the anterior jugular chain. Notice the relationship of these lymph nodes with the last four cranial nerves and the cervical sympathetic in the retropharyngeal space.

lesion It easily spreads to the petrosphenoidal region of the base of the skull It does not, however, grow rapidly enough to cause symptoms from compression of the nerve, although the nerve may be surrounded by tumor It is only late in the development, long after tumor has spread into the middle cerebral fossa, that it decalcifies the bones of the base of the skull In very advanced stages, tumor may invade the orbit through the inferior orbital fissure and may invade the maxillary sinus most commonly through the ethmoid

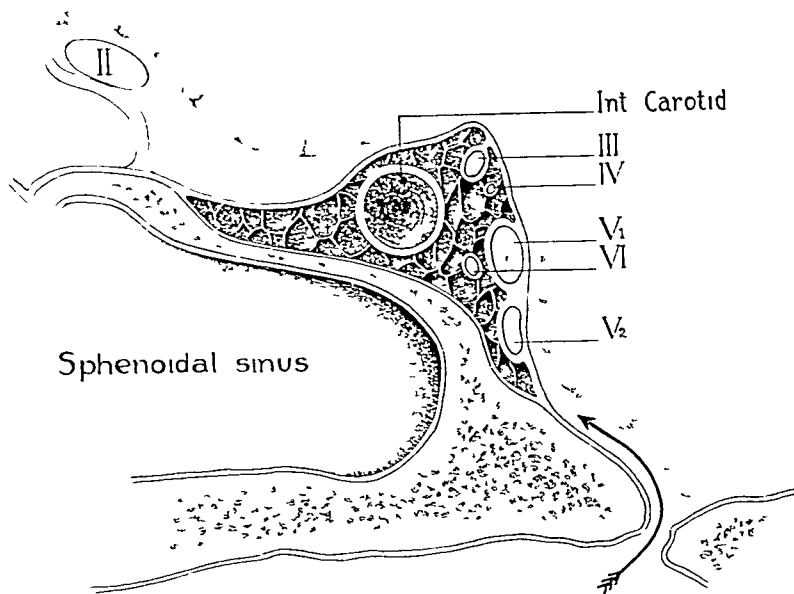


Fig. 239—Schematic representation of an oblique section of the base of the skull passing through 1 the sphenoidal sinus and 2 the cavernous sinus. The arrow illustrates the way in which tumors of the nasopharynx come rapidly in contact with the third fourth fifth and sixth cranial nerves which are in the substance or in the lateral wall of the cavernous sinus

The *exophytic* type of growth is usually a hemispheric, nonulcerated sometimes pedunculated, smooth tumor which may arise from the roof and rapidly fill the nasopharyngeal cavity. It pushes the soft palate downward and spreads toward the choanae and the nasal fossa (Fig. 245). It rapidly reaches the maxillary sinus and the orbit, producing marked unilateral exophthalmus. This exophytic tumor has even been seen protruding through the anterior nares. This form of development is typical of lymphosarcomas of the pharyngeal tonsil. Those lymphosarcomas which develop from the eustachian tube area do not show much tendency to grow toward the nasopharyngeal cavity but spread in the submucosa toward the base of the skull. They do not compress the cranial nerves until they become quite bulky, and even then the nerve paralyses are few and limited. Erosion of the base of the skull is also seldom observed in lymphosarcomas. In contrast with the two previous forms, those

sarcomas of the nasopharynx are all most commonly found in patients 40 to 45 years of age. Epidermoid carcinomas are rarely seen in patients under 25 years and lymphoepitheliomas may occasionally be encountered in young individuals, but lymphosarcomas are seen both in children and in the very aged.

Approximately two thirds of all tumors of the nasopharynx occur in males, but this incidence is gradually reduced to about one half of all cases as one passes from the epitheliomas through the lymphoepitheliomas to the lymphosarcomas.

The Chinese have an unusual predisposition to the development of cancer of the nasopharynx, particularly lymphoepitheliomas and lymphosarcomas. Digby reported that during eight years at Hong Kong University, 114 cases of cancer of the nasopharynx were seen, while only 74 carcinomas of the breast and 174 carcinomas of the cervix were observed during the same period. This high incidence of tumors of the nasopharynx in Chinese has been attributed to their living habits. However, Chinese who are born and raised in America have a greater tendency to develop this form of cancer than has any other racial group in the Western Hemisphere. Martinez reported 29 per cent of Chinese patients among those affected with cancer of the nasopharynx at the Cancer Institute of Havana.

### Pathology

**Gross Pathology**—Grossly, tumors of the nasopharynx may develop into three very distinct categories: (1) ulcerated, (2) lobular, (3) exophytic.

The *ulcerated* lesions are most frequently found on the posterior wall or deep in the Rosemüller's fossa. Less frequently they are situated on the lateral wall in front of the eustachian tube or on the roof of the nasopharynx. These rare ulcerated lesions are often well differentiated epidermoid carcinomas. The ulcerations are small and necrotic and progressively infiltrate the neighboring tissues. Those which develop on the lateral wall or on the roof of the nasopharynx are canalized by the pharyngeal fascia toward the petrosphenoidal region of the base of the skull. They tend to destroy and enlarge foramina and spread into the middle cerebral fossa. There they may remain subdural or may invade the dura and the bones. The invasion of the petrous portion of the temporal bone is rare. In this area the tumor comes into contact with several cranial nerves (II, III, IV, V, VI), which are compressed but not necessarily invaded (Fig. 239).

The *lobulated* form of nasopharyngeal tumors arises most commonly from the eustachian tube area which becomes rapidly obliterated. The tumor has a grapelike polypoid appearance and may not show ulceration anywhere on its surface. More commonly, however, a small ulceration in great disproportion with the size of the tumor is visible (Fig. 244). This form of development is usually observed in a lymphoepithelioma or a very undifferentiated epidermoid carcinoma. The tumor infiltrates around the eustachian tube and when it spreads forward, may extend into the maxillopharyngeal space and compress the mandibular branch of the fifth cranial nerve. In spreading downward it may interfere with the normal excursion of the soft palate on the side of the



### Clinical Evolution

The nasopharynx is the most frequent blind spot in the diagnosis of all tumors of the aerodigestive tract (Canttil). The majority of patients with malignant tumors of the nasopharynx are seen because of a cervical adenopathy without any symptoms referable to a primary lesion in the nasopharynx. The next most common symptoms are hypoacusia, nasal obstruction, cranial nerve paralysis, and pain.

A unilateral, painless, upper cervical *adenopathy* is often the first sign of the disease, the metastatic nodes usually developing in the submastoid area. Nodes of the internal jugular chain following the course of the sternocleidomastoid muscle may also be invaded. It is not uncommon, however, to have consecutive involvement of nodes of the spinal chain following the anterior border of the trapezius muscle. The lymphadenopathy is most often unilateral, rapidly growing, bulky (6, 8, or 10 cm in diameter), somewhat lobulated, and accompanied by considerably smaller nodes in the corresponding chain. This is the typical lymphadenopathy of lymphoepitheliomas or very undifferentiated epidermoid carcinomas. The very rare cases of differentiated carcinomas present a small, rounded adenopathy, usually confined to the upper cervical region. In lymphosarcomas, the adenopathy may be unilateral or bilateral, depending on whether the tumor arises from the lateral wall or on the roof and posterior wall of the nasopharynx. These also grow rapidly but are considerably softer and quickly extend to other elements of the spinal and internal jugular chains. In some cases of lymphosarcoma, the cervical adenopathy may be discrete, while other metastatic nodes of the mediastinum or retroperitoneal regions may be considerably larger.

A unilateral diminution in the sense of hearing, *hypoacusia*, is very commonly found accompanying tumors of the nasopharynx, but especially in lymphoepitheliomas and lymphosarcomas. This is, of course, due to an obliteration of the internal orifice of the eustachian tube. The hypoacusia may be so insidious that the impairment of hearing may not have been noticed. A certain number of patients will give a history of long-standing, unilateral hypoacusia. This is sometimes connected with long-standing chronic inflammatory lesions which may have contributed to the development of the tumor.

A definite *nasal twang* in speech is sometimes noticed, a consequence of the lack of nasopharyngeal resonance, obstruction of the choanae, and mechanical interference with the normal movements of the soft palate. *Nasal obstruction* is not infrequent in lymphosarcomas. *Nasal bleeding* or retropharyngeal bleeding is a rare occurrence. *Pain* results from compression of the trigeminal nerve or its branches and from invasion of the bones of the skull. The character of the pain is usually related to the motor paralyses which also result from the compression of the fifth nerve. They will be described together.

Trotter described a triad of symptoms which he thought were associated with "endotheliomas" of the tubal area. This triad consists of (1) hypoacusia, (2) impaired movements of the soft palate, and (3) neuralgia along the territory of the mandibular nerve. Trotter's clinical description of this triad fits perfectly the development of a lymphoepithelioma of the eustachian

lymphosarcomas which develop in the Rosenmüller's fossa may not be very large and remain unchanged for a considerable length of time without giving any signs of their presence

**METASTATIC SPREAD**—A metastatic adenopathy is usually present with every tumor of the nasopharynx. The retropharyngeal nodes are often invaded particularly in tumors of the roof and posterior and lateral walls of the nasopharynx, but they seldom become very large when involved from tumors of the lateral wall. An early metastasis may be found in the Krause group of nodes, which are very highly placed close to the last four cranial nerves and the cervical sympathetic as they emerge from the base of the skull. As these nodes enlarge compression of the nerves with a resulting paralytic syndrome takes place (Regito). From the Krause group of nodes, lymphatic permeation leads to the nodes of the internal jugular chain, and not infrequently to the spinal chain of nodes placed just beneath the trapezius muscle behind the jugular chain which follows a divergent direction.

From the neck metastatic tumor may continue to the lymphatics of the next relay (axilla, mediastinum). With lymphosarcomas, which are generalized, practically no lymph node is exempt from invasion. In generalized cases of lymphoepitheliomas blood borne metastases to the lungs, liver, and bone are rather frequent (Chin), while this is only the exception in epidermoid carcinomas and extremely rare in lymphosarcomas.

Death occurs from generalization of the tumor and resulting cachexia. In a few cases of differentiated carcinomas death may result from hemorrhage, meningeal complications, or general debilitation due to pain, while the disease remains rather localized to the base of the skull.

**Microscopic Pathology**—It is generally admitted that lymphosarcomas are rather frequent, making up from one third to one half of all primary tumors of the nasopharynx. On the other hand, very differentiated epidermoid carcinomas of the nasopharynx are exceptional. The remaining number is represented by a rather large group of tumors mostly lymphoepitheliomas which are variously diagnosed as undifferentiated epidermoid carcinomas, transitional cell carcinomas, lymphoepitheliomas and even lymphosarcomas.

The differentiated squamous cell carcinomas of the nasopharynx are clear cut diagnostic entities. The difficulty in microscopic diagnosis lies with the larger number of anaplastic undifferentiated epidermoid carcinomas. A good number of them may fall into what Quick and Cutler have called *transitional cell epidermoid carcinomas*. These tumors consist of masses of small round or polyhedral cells with a large hyperchromatic nucleus which occupies almost the entire cell. These cells have great variation in staining qualities and they have a tendency to grow in anastomosing cords or sheets without any tendency to keratinization. The name "transitional cell carcinomas" suggests the possibility that these tumors arise from the transitional epithelium of the gland ducts. This is, of course, hypothetical. Other authors prefer to group these cases under the name of *anaplastic epidermoid carcinomas*.

Regaud and Schmincke, in 1921, simultaneously but independently described a new form of tumor which was called *lymphoepithelioma*. Regaud





PLATE V

Lympho sarcoma of the nasopharynx in a young child. First manifestation of the disease was ocular nerve paralysis. (From Burford, W. N., Ackerman, L. V., and Robinson, H. B. G. *Am J Orthodontics and Oral Surg* 1944.)

palpebral fissure, enophthalmia, and myosis characteristic of the Horner's syndrome due to compression of the cervical sympathetic (Fig 248)

There are instances in which the paralysis of the last four cranial nerves and the sympathetic do not coincide, and limited syndromes only may be present. The syndrome of Jackson, as described by him, is a hemiparalysis of the soft palate, larynx, and tongue, which would correspond to a compression of the eleventh and twelfth cranial nerves. Such is also the case when only the ninth, tenth, and eleventh nerves are compressed, resulting in a syndrome of the jugular foramen (Vernet). There may be, in addition to these three nerves, also a paralysis of the hypoglossal nerve without any evidence of compression of the cervical sympathetic (Collet, Siread)

The natural evolution of malignant tumors of the nasopharynx which are not controlled is mostly toward the generalization of the disease. In epidermoid carcinomas, however, invasion of the meninges, hemorrhage, and secondary infection or severe pain and deterioration of the general condition may be observed at the terminal stages without generalized metastases. In lymphoepitheliomas, lung, bone and liver metastases are not rare. In lymphosarcomas the generalization is mostly in the lymphatic system. In infants lymphosarcoma metastasizes rapidly to the mediastinum and then it is not infrequent that lymphosarcomatous cells may pass into the circulation, giving an impression of acute leucemia, which has been called leucosarcoma (Steinberg, Wiseman)

### Diagnosis

It is only in the past fifty years that tumors of the nasopharynx have been correctly diagnosed due to the progress of otolaryngology. However, even today many cases pass undiagnosed. To illustrate the difficulty with which this entity is recognized, New reported that in 194 of his patients with malignant lesions of the nasopharynx, 185 operations were done before the correct diagnosis was established. These operations included trepanation of sinuses, removal of nasal polyps and turbinates, mastoidectomies, myringotomies, alcohol injections, and teeth extractions. Errors in diagnosis are due primarily to disregard of the pharynx at examination. Actually, this examination does not require special skill or instruments. In addition, it has not been sufficiently emphasized that patients with cervical adenopathy, particularly those between 30 and 50 years of age but also in younger and older patients, may have a primary tumor of the nasopharynx. A safe approach will be to assume the presence of such a primary nasopharyngeal lesion in all patients with metastatic tumor of the upper cervical region unless otherwise demonstrated. This statement is reinforced by the fact that more than half of all primary tumors of the nasopharynx have a clinical onset by the development of cervical adenopathy.

**Method of Examination**—No examination of the nasopharynx should be done without a previous inspection of the oral cavity, oropharynx, hypopharynx, and larynx. This may reveal an impairment of the movements of the soft palate due to the presence of a tumefaction behind it. In addition, it may

tube with forward extension, interfering mechanically with the movement of the soft palate and irritating the mandibular branch of the fifth nerve in the maxillopharyngeal space. *Cranial nerve paralyses* are not frequently the first symptoms of tumors of the nasopharynx, except in children (Plate V) but they are not uncommon later in their development. In a large series of patients with cancer of the nasopharynx, Godtfredsen found 38 per cent presenting neurologic symptoms. The percentage is doubled in children. These cranial nerve paralyses appear most often in the form of two syndromes: (1) the petrosphenoidal syndrome of Jacod, produced by direct extension of the neoplasm, and (2) the syndrome of the retroparotidian space of Villaret due to the development of the metastatic adenopathy (Regato). A unilateral paralysis of all of the cranial nerves has sometimes been observed in patients with advanced cancer of the nasopharynx (Lyonnet). In general however such extensive paralyses are associated with neoplasms of the base of the skull proper, such as fibrosarcoma and osteogenic sarcoma (Garçin).

The *petrosphenoidal syndrome* results from the compression of the second, third, fourth, fifth, and sixth cranial nerves and consequently is characterized by unilateral neuralgia of the trigeminal type with total unilateral ophthalmoplegia and amaurosis. As a general rule, this syndrome starts by sudden paralysis of the abducens (VI) and by pain in the supraorbital and superior maxillary regions (V). Unless treatment is administered at this time the syndrome rapidly progresses with a palpebral ptosis, fixation of the eye, and finally loss of sight (Figs 246 and 247). The sensory troubles due to compression of the fifth nerve pass through various stages. As a general rule there is pain first and then hyperesthesia of the cutaneous territory of the ophthalmic and superior maxillary nerves. The pain seems to center around the floor of the orbit. In the mouth there may be a painful anesthesia of one side of the tongue, floor of the mouth, and buccal mucosa. The motor difficulties resulting from compression of the mandibular branch result in paralysis of the temporal, internal pterygoid, and masseter muscles. These muscles become atrophied after the paralysis has been present for some time, and, as a consequence, there may be a slight asymmetry of the face which could be taken for a facial paresis.

The *syndrome of the retroparotidian space* results from the compression of the ninth, tenth, eleventh, and twelfth cranial nerves and the cervical sympathetic. This is usually the consequence of the development of retropharyngeal or retroparotidian metastases which compress these nerves as they emerge from the base of the skull. The compression of these nerves results in difficulties in deglutition because of hemiparesis of the superior constrictor muscle in perversion of the sense of taste in the posterior third of the tongue (IX), and in a hyperesthesia, hyposthesia or anesthesia of the mucous membrane of the soft palate, pharynx and larynx and in respiratory troubles and salivary troubles (X). In addition, there is a paralysis and atrophy of the trapezius and sternocleidomastoid muscles as well as a hemiparesis of the soft palate (XI) and a hemiparalysis and atrophy of one side of the tongue (XII). All of this is usually accompanied and sometimes preceded by a narrowing of the

ing of the posterior wall of the pharynx, the soft palate, and the floor of the nasal fossa with an anesthetic solution, an interval of a few minutes should be allowed to elapse. Then a rubber catheter (urethral catheter, French 12) can be introduced through one of the nostrils on the opposite side of the suspected lesion while the patient breathes deeply with his mouth open. As soon as the tip of the catheter is visible behind the soft palate, it may be grasped with a clamp and brought outside the mouth. By progressively tightening this elastic catheter, the soft palate will be brought forward and a very satisfactory posterior rhinoscopy will be possible with a large laryngeal mirror (Fig 241)

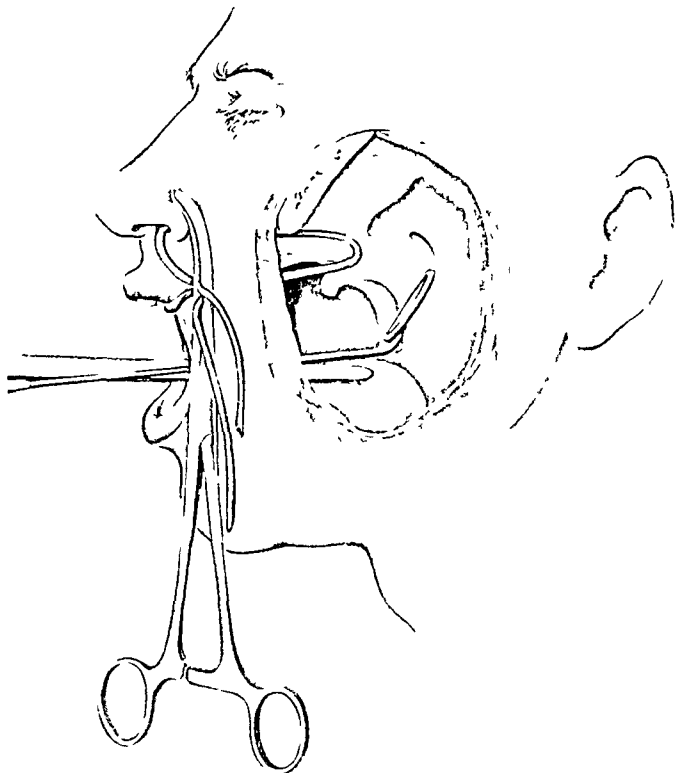


Fig 242—Progressive retraction of the soft palate by the rubber catheter permits wide view of the nasopharynx without great discomfort to the patient

In general, the introduction of one catheter is sufficient, but a very perfect view can be had by duplicating the procedure on the other side. It is more satisfactory for this examination that the examiner be provided with a head light rather than with a reflecting head mirror.

A posterior rhinoscopy will allow a wide view of the choanae and the posterior extremities of the middle and lower turbinates. Opaline areas of

reveal the presence of a paralysis of the soft palate, pharynx, and larynx due to compression of the cranial nerves

A very simple method of examination of the nasopharynx is the *digital exploration*. This can be done without anesthesia but is considerably easier if done after spraying the area with an anesthetic solution. Palpation of both sides of the nasopharynx may reveal asymmetry, indurations, or tumefactions. An inspection of the pharynx should always be made following palpation, as some tumors bleed after manipulation. The examination of the nasopharynx

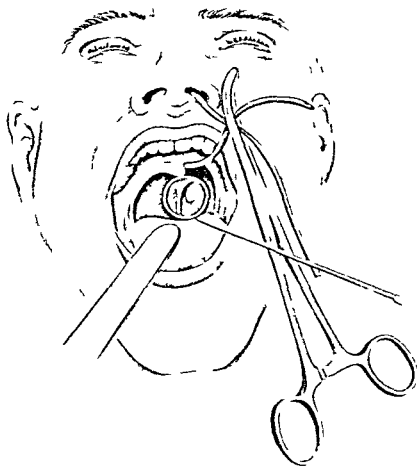


Fig. 241.—The easiest way to examine the nasopharynx is to insert through the nostril a rubber catheter which is retrieved behind the soft palate by means of a forceps and brought out of the mouth where it is kept tense by means of a clamp. Only a light spray anesthesia is necessary.

by means of a mirror the *posterior rhinoscopy* is sometimes possible where there is a large retrovelar space and subnormal pharyngeal reflexes. A marked anesthesia of the soft palate and pharynx should lead to the suspicion that the vagus nerve is being compressed by tumor. A posterior rhinoscopy, however, is best accomplished by means of a soft palate retractor (the most common model in use is the Harsinger soft palate retractor). The general practitioner nevertheless can make a very thorough exploration of the nasopharynx without the help of any special instrument. After a thorough spray



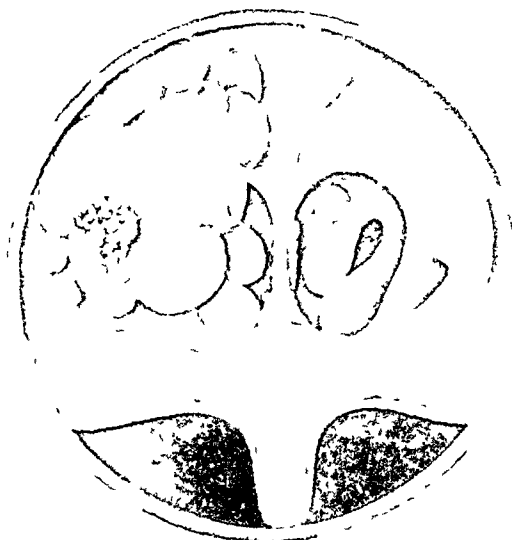


Fig. 244—Lymphoepithelioma of the right Eustachian tube area showing a polylobated out growth with little ulceration. Undifferentiated carcinomas have a similar appearance.

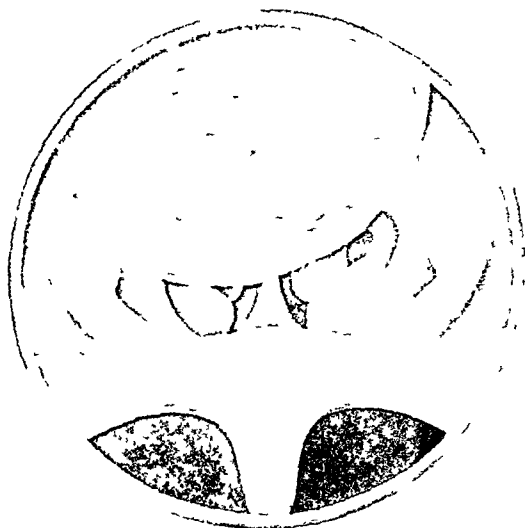


Fig. 245—Lymphosarcoma of the roof of the nasopharynx showing ulceration and bilateral obstruction of the choanae. Lymphosarcomas arising in Rosenmüller's fossa seldom become very large and are usually discovered only after distant metastases are evident.

lymphoid tissue may be seen developing in the floor of the nasal fossa or on the sides or the septum in normal individuals and should not be mistaken for tumor. A better view of the lateral walls of the nasopharynx may be obtained by displacing the examining mirror to one or the other side. Outgrowth tumefactions may be seen easily but submucous nonulcerated infiltrations and deeply ulcerated lesions in the Rosenmüller's fossa and roof of the nasopharynx may require repeated examinations. Because of the numerous anatomic variations of the normal nasopharynx, the symmetry of the two sides should be noted.

The *endoscopic examination* by means of a specially designed instrument has been advocated by some authors. The difficulties of this type of examination are those common to all forms of endoscopic examination. The examiner will have a monocular view and very little sense of distance. This type of examination cannot replace a thorough posterior rhinoscopy but it has its indications and is a valuable additional means of examination in competent hands.



Fig. 243—Carcinoma of the roof and lateral wall of the nasopharynx showing extensive erosion of bone.

**Radiographic Examination**—The radiographic examination is a valuable adjunct in the diagnosis of malignant tumors of the nasopharynx. A profile view of the skull sometimes offers additional information as to the location and extension of tumors of the posterior wall and roof of the nasopharynx. Invasion of the sphenoid bone and sphenoidal sinus may also be evident by this profile roentgenogram. In addition, examination of the base of the skull (submental vertex) will offer the possibility of comparison to the normal size and may reveal the presence of 'punched-out' decalcifications of the bone. These areas of bone destruction are most often found around the foramen

*Olfactory* (I) —This nerve is seldom compressed by nasopharyngeal tumors unless the disease has become very extensive. In addition, it is always difficult to ascertain the presence of a unilateral deficiency of the olfactory sense, particularly when there is also nasal obstruction.

*Optic* (II) —The compression of the optic nerve results in complete unilateral amaurosis. The nerve is usually compressed between the chiasm and the optic foramen just medial and anterior to the cavernous sinus.

*Oculomotor* (III) —Compression of this nerve results in paralysis of the upper, lower, and inner rectus muscles of the eye also of the inferior oblique and levator palpebrae. This causes complete fixation of the eye except for its lateral movement, and it also causes palpebral ptosis. The nerve is usually compressed inside the cavernous sinus or on its lateral wall.



Fig. 246 —Carcinoma of the nasopharynx with palpebral ptosis produced by compression of the third cranial nerve.

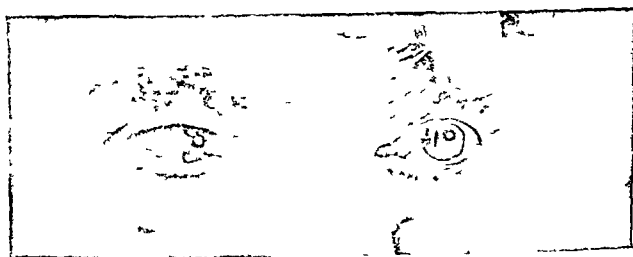


Fig. 247 —Same patient showing complete fixation of the left eye due to compression of the third, fourth and sixth cranial nerves.

*Trochlear* (IV) —This is the nerve of the superior oblique muscle of the eye and its compression results in paralysis of that muscle. Rarely observed alone, it most often accompanies compression of the oculomotor in the cavernous sinus.

*Trigeminal* (V) —This is both a motor and sensory nerve which divides into three branches: (1) the ophthalmic, (2) the superior maxillary, and (3) the mandibular. Of these, the first two branches are strictly sensory, but the latter is both sensory and motor. All three branches may be compressed at their origin in the gasserian ganglion. The mandibular branch may be compressed alone in the maxillopharyngeal space.

lacerum and foramen ovale (Fig 253) In cases where there is invasion of the nasal fossa, ethmoids, and orbit, an anteroposterior view will also contribute information

The final diagnosis of any one of the different pathologic entities which may develop in the nasopharynx is, of course, a microscopic one, but there are very eloquent clinical signs which may give a strong suspicion of the entity in question A clinical onset by development of cervical adenopathy is most often connected with lymphosarcomas and lymphoepitheliomas, a bilateral adenopathy, particularly early in the history, is almost always associated with lymphosarcomas, hyposcousia is a common symptom which may be present with the different tumors of the nasopharynx, but nasal obstruction, particularly when bilateral, is most often a sign of lymphosarcoma Rapid invasion of the nasal fossa, ethmoid, and orbit may be found both with lymphoepitheliomas and lymphosarcomas, but it is faster and is found earlier in the development of lymphosarcomas Cranial nerve paralyses are almost constantly found in epidermoid carcinomas, but they are not infrequent in lymphoepitheliomas and even lymphosarcomas, particularly in children The difference here is perhaps in the intensity of the trigeminal pain which may be very mild in lymphoepitheliomas and very severe in epidermoid carcinomas These paralyses are present only in the last stages of development of lymphosarcomas and always in an abortive form Nasal and postnasal bleeding is an almost exclusive sign of differentiated carcinomas Distinct metastases may be present in lymphoepitheliomas and lymphosarcomas, but when they are found in the lungs, liver, and bone the chances are great that the lesion is a lymphoepithelioma They are most frequently found in the spine, pelvis and femurs (Ch'lin) Distinct metastases are very infrequent in epidermoid carcinomas

**Biopsy**—These tumors which are exophytic and project into the nasopharyngeal cavity facilitate the obtention of specimens for microscopic examination A specimen is best procured through the nasal fossa by means of a straight forceps If necessary, the removal of the specimen may be controlled by posterior rhinoscopy For those tumors which infiltrate deep into the Rosenmuller's fossa and roof of the nasopharynx and which do not have any outgrowth, the specimen is best secured by means of a curved forceps introduced behind the soft palate Unfortunately in some instances a positive specimen is unobtainable and the diagnosis may have to rely on the description of the primary tumor and on the pathologic examination of the often present cervical metastases

An aspiration biopsy of the metastatic nodes is usually satisfactory for establishing the diagnosis of malignant tumor When the diagnosis of the primary lesion has previously been established an aspiration biopsy of its metastases should be done as a matter of record

**Cranial Nerve Paralysis**—Cranial nerve paralyses are not of course, an exclusive feature of nasopharyngeal tumors In order to be able to make a differential diagnosis a thorough knowledge of the symptoms produced by the compression of each nerve is necessary

Compression of sensory fibers of the fifth nerve results in neuralgic pain of the supraorbital and superior maxillary regions. This may be accompanied by hyperesthesia and followed by hypoesthesia and anesthesia. In the mouth, there is most often "painful anesthesia" of half the tongue, floor of the mouth, buccal mucosa, and hard palate.

The compression of the motor fibers of the mandibular branch results in paralysis of the temporal, internal pterygoid, and masseter muscles. This is evidenced by the inability to protrude the lower jaw so as to bring the lower teeth in front of the upper teeth. The total compression of the fifth nerve is evidenced by the lack of corneal reflex.

*Abducens* (VI) —Compression of this nerve produces paralysis of the external rectus muscle of the eye which results in diplopia and internal strabismus. The abducens nerve is very vulnerable because of its long subdural trajectory, and it is the most sensitive of all the cranial nerves.

*Facial* (VII) —Compression of the facial nerve causes a typical peripheral facial paralysis. However, it is well protected by the petrous portion of the temporal bone and is seldom compressed by nasopharyngeal tumors.

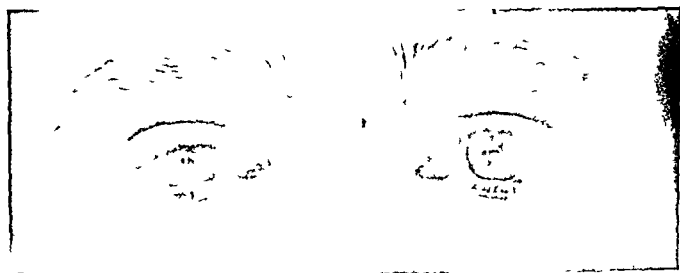


FIG. 249—Horner's syndrome as a presenting symptom of a tumor of the right side of the nasopharynx.

*Acoustic* (VIII) —Compression of this nerve results in loss of hearing and in vertigo. Evidence of its compression requires special verification. This nerve is also rarely reached by nasopharyngeal tumors.

*Glossopharyngeal* (IX) —There is still considerable discussion as to the resulting abnormalities from compression of the glossopharyngeal nerve. According to Vernet, its compression results in a paralysis of the constrictor superior muscle of the pharynx. This paralysis of the constrictor superior may be evidenced by a transversal movement of the posterior wall of the pharynx (certain movement of Collet) when a pharyngeal reflex occurs. This would be due to a unilateral contraction of the constrictor superior. The sensory troubles will be characterized by a perversion of the sense of taste on the posterior third of the tongue.

Caussé, in reviewing a number of cases with injuries or experimental division of the glossopharyngeal nerve, failed to find the "certain sign" in any of them but agreed that the sense of taste of the base of the tongue was probably regulated by this nerve, although the exact territory is very variable.

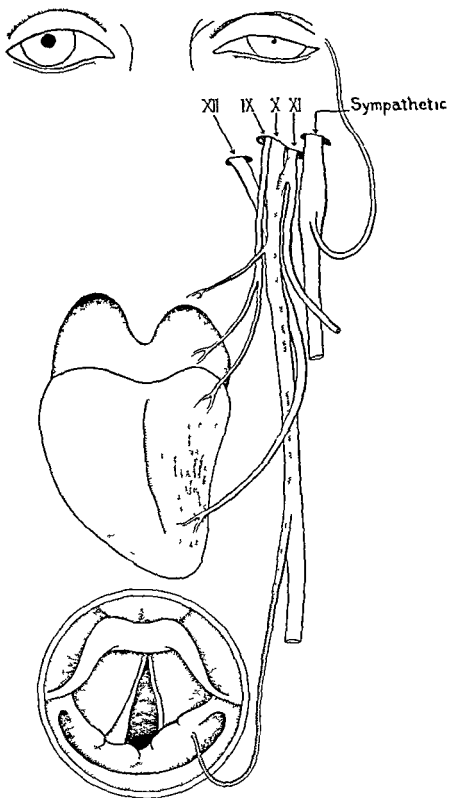


Fig. 248—Schematic illustration of the distribution of branches of the last four cranial nerves and the cervical sympathetic in reference to their compression by tumors of the nasopharynx. The compression of all these nerves results in a Horner's syndrome, hemiparalysis of the soft palate and of the wall of the pharynx, hemiparalysis of the tongue and hemiparalysis of the larynx, plus sensory disturbances.

and in a hemiparalysis of the soft palate and larynx of the same side (internal branch). As a result of this compression, there will be atrophy of the cervical muscles, lowering of the arch of the soft palate, and dysphonia.

*Hypoglossal (XII)*—This is a purely motor nerve innervating half of the tongue. Its compression results in rapid atrophy of one side of the tongue which, in protrusion, will deviate toward the paralyzed side (Fig. 250).

*Cervical Sympathetic*—This nerve provides the fibers going to the orbital fascia and those which are responsible for the dilation of the iris. Its compression results in a constriction of the pupil, a retraction of the eye into the orbit, and a consequent narrowing of the palpebral fissure, known as Horner's syndrome (Fig. 249).

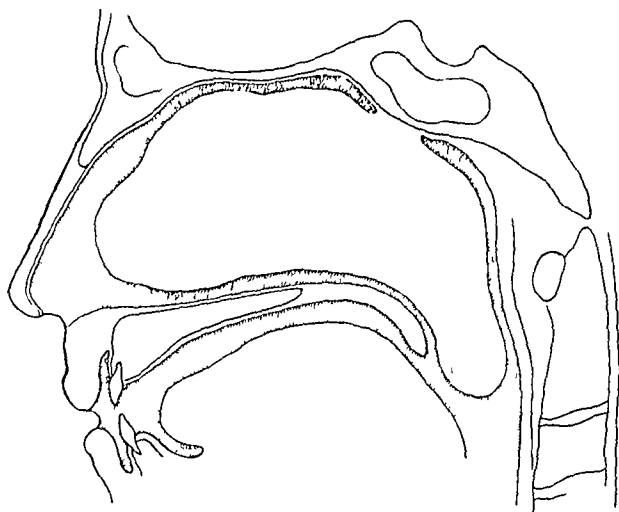


Fig. 251—Sketch of a nasopharyngeal fibroma illustrating its pedunculated attachment to the base of the skull and its well-encapsulated extension toward the nasal fossa and toward the pharynx.

**Differential Diagnosis**—A paralysis of the facial (VII) may be present in the course of *acute otitis media*, together with some irritation of the trigeminal nerve (V). In such cases, however, the temporal pain is predominant and there is an elevation of temperature. The otitis seldom includes compression of other nerves. Facial nerve paralysis is seldom due to a nasopharyngeal tumor unless the tumor is in the last stages of its development. When a paralysis of the facial nerve is accompanied by loss of hearing and vertigo, nystagmus, cerebellar symptoms, nausea, choked disk, and symptoms of compression of the fifth, ninth, tenth, or eleventh nerve, the diagnosis should turn toward a possible tumor of the acoustic nerve. In the presence of an ophthalmoplegia without evidence of compression of the fifth nerve, the disturbance will probably be found in the orbit itself and is most often produced by benign bone tumors.

According to him, the division of the glossopharyngeal nerve results in a lowering of the arch of the soft palate. It is not demonstrated, however, whether these motor fibers originate, as they may, in the spinal accessory nerve.

**Vagus (X)**—There has been confusion as to the physiology of this nerve. The work of Vernet established the fact that the vagus is an entirely sensory nerve and that all of its motor fibers which go to the pharynx, larynx, and heart originate in the spinal accessory and pass to the vagus through an anastomosis in the base of the skull. Compression of the vagus is responsible for the anesthesia of the soft palate, pharynx, and larynx which results in passage of food into the trachea and consequent cough. In addition, there may be cardiorespiratory difficulties such as tachycardia and trachypnea. Congestive lesions of the base of the lung on the same side as the nasopharyngeal lesion have been attributed to vasomotor and trophic disturbances due to compression of the vagus. In addition, there may be hypersalivation or hyposalivation but these are very inconstant.



FIG. 20. It is paralysis and atrophy of the left side of the tongue caused by a carcinoma of the lateral wall of the nasopharynx.

A hyperesthesia of the tragus of the ear is a very good sign of compression of the vagus nerve, the cutaneous fibers of which go to the external auditory canal.

**Spinal Accessory (XI)**—This nerve is strictly a motor nerve and supplies the vagus with its motor fibers. Compression of this nerve results in paralysis and atrophy of the trapezius and sternocleidomastoid muscles (external branch).



**diagnosis** This is the *nasopharyngeal fibroma* which is predominantly found in boys between 10 and 16 years of age although rare cases have been seen in men up to 30 years of age. These tumors arise at the union of the roof and posterior wall of the nasopharynx (Fig 251) in the form of a shiny nonulcerated rubbery tumor. It may finally fill the nasopharyngeal cavity extend to the nasal fossa and even to the maxillary sinuses and protrude through the nares (Fig 252). Biopsies and incomplete excisions are often followed by serious hemorrhage rapid recurrences and the creation of new adhesions in addition to its natural pedicle. Microscopically, these tumors are fibromas, and it has been noticed that the majority of them regress spontaneously after the age of 25 years. For this reason and because of their aggravation following excision these tumors should be treated by external roentgentherapy or interstitial curietherapy which results in marked but rather slow regression with moderate doses. This conservative treatment seems to be justified in view of the results obtained. Tumors of the mucous and salivary gland type are occasionally found in the nasopharynx. They develop mostly from the roof and Rosenmüller's fossa and may invade the base of the skull to give cranial nerve paralysis. These tumors have a rather benign slow development although they may actually be malignant. They may react favorably to irradiation but are not sterilized by this form of treatment.

### Treatment

Before the advent of radiotherapy a multitude of surgical techniques were applied to the treatment of tumors of the nasopharynx. These elaborate surgical procedures by oral nasal or transfacial approach were then justified. Actually no matter how favorable the conditions and the means of approach the complete surgical extirpation of these tumors even in their earlier stages is an impossibility. In addition their common anaplastic features and production of early metastases make them unfavorable for surgical treatment.

**ROENTGENTHERAPY**—The main difficulty in the treatment of malignant tumors of the nasopharynx by external irradiation lies in the fact that these tumors are deep and it is necessary for the radiations to pass through a large thickness of dense tissue which absorbs most of them. This difficulty however may be obviated by multiplying the portals of entry and thus adding from different directions a sufficient total dose for sterilization. Two lateral fields are commonly used. In addition two superior maxillary fields may be useful with the beam in an anteroposterior or oblique direction depending on the situation of the lesion. In cases of anterior extension of the tumor and in all cases of lymphosarcoma a nasal field strictly anteroposterior is indicated because of the usual recurrences in the ethmoids and nasal fossa. Irradiation of nasopharyngeal tumors through the necessarily small perioral field is unjustified in most instances with the exception perhaps of tumors developing rather low on the posterior wall of the nasopharynx. Another obstacle is the inability to bring to the level of the tumor a large daily dose but this is only a disadvantage in the very differentiated types of carcinoma which require such daily dosage. In the majority of cases a protracted treatment with

Individual lesions or paralytic syndromes of the last four cranial nerves and cervical sympathetic have been reported as a result of injuries (particularly war injuries), but paralysis of these nerves may occur in the course of inflammatory conditions of the middle ear with an adenopathy in the retro parotidian space or a possible phlebitis of the jugular vein. Here, again, the cause of the paralysis will be betrayed by the typical acute inflammatory picture of the case. Salivary gland tumors of the parotid may come in direct contact with the last four cranial nerves in the retroparotidian space and produce a compression of these nerves, and the same is true of nasopharyngeal chordomas. Both of these tumors, however, present a very slow growth, and this factor will help in the differential diagnosis. Chordomas are malignant tumors which develop at the expense of vestigial remnants of the notochord; they may appear in the nasopharynx as they do in the sacrococcygeal region (see *Sarcomas of Soft Tissues* page 1014). They have a typical histologic appearance presenting a definite radiosensitivity, but are seldom cured in the nasopharynx (Rupert). Cranial nerve paralysis may occur as a consequence of syphilitic meningitis but in these cases very often the paralyzes are bilateral and they do not follow a particular group pattern, or syndrome. They seem to attack, in particular, the ocular muscles and the trigeminal nerve. The specific reactions in the blood and the spinal fluid will be of help in establishing the diagnosis of syphilis. Intracranial tumors may also give cranial nerve paralysis, but these are constantly accompanied with symptoms of compression of the pyramidal tract and increased intracranial pressure.

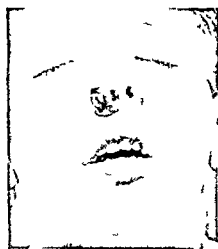


Fig. 22.—Nasopharyngeal fibroma protruding through the right nostril in a boy 12 years of age

There are but few benign conditions of the nasopharynx which may be mistaken for malignant tumors. In children one should be aware of the often exaggerated pharyngeal tonsil, which may be unusually large in some cases (adenoids). The adenopathy which accompanies these benign conditions of the nasopharynx is usually discreet, bilateral, multiple, and tender.

There is a benign tumor of the adolescent male, more common in European countries than in the United States which may offer some difficulties in

in some instances, probably because of invasion rather than compression of the gasserian ganglion, an intense pain of the trigeminal territory will persist and require continuous administration of narcotics

The most common cause of failure in the treatment of these tumors and their metastases is underdosage. A large proportion of failures is due to the development of distant metastases.

During the course of treatment, a radioepithelitis of the mucous membrane and a radioepidermitis of the skin (requiring special care) may develop. Because of the treatment of nodes, the radioepithelitis of the hypopharynx will cause dysphagia and loss of weight, but, in general, a well-balanced high caloric, high vitamin, liquid diet will suffice.

The most common complication in the course of treatment is an otitis media with its characteristic intense pain and rapid elevation of temperature. This will almost always react favorably to the administration of sulfonamides or penicillin.

**CURIOUS HISTORY**—Because of the lack of sufficient penetration of radiations of 200 kv. equipment, most radiotherapists have looked for additional irradiation by means of radium introduced into the nasopharyngeal cavity. Blady has devised an ingenious instrument by which this may be accomplished. This type of irradiation, however, is rather inaccurate and lacks the homogeneity of distribution which is always desirable in the treatment of cancer. A thorough exhaustive external irradiation by all possible portals of entry is equally successful and considerably more satisfactory. Lenz treated his patients with external roentgentherapy alone, Martin and Blady routinely combined external irradiation with intracavitary curietherapy. The results in both series are about the same.

Interstitial implantation of radon seeds in the metastatic cervical nodes has also been suggested as an adjunct to external irradiation. Here, again, it might be useful to remember that the majority of failures in the treatment of cancer of the nasopharynx are not due to lack of sterilization of the cervical lymph nodes but rather to the inability to control the primary lesion or to the development of distant metastases. If the possibilities of external irradiation are exhausted, an additional implantation of radon seeds is useless. If the external irradiation has been insufficient, the implantation of seeds can rarely bring a necessary minimum total dose to the entire tumor area.

### Prognosis

The prognosis of cancer of the nasopharynx in the adult is considerably better today than it has been in the past. The outcome is almost always fatal in children. Godtfriksen compiled 266 cases of cancer of the nasopharynx from four Scandinavian institutions and found fifty-nine (22 per cent) of the patients living and well five years after radiation therapy. Baclesse reported sixteen patients living and well at the end of four years in a series of 102 patients treated at the Foundation Curie.

Among the different histologic entities, lymphosarcoma seems to have the best prognosis. Lenz reported five patients cured of ten treated for lympho-

moderate daily dosage is sufficient to sterilize the primary lesion. With the use of supervoltage equipment (800,000 to 1,000,000 volts), a higher daily dose should reach the region of the tumor, but in most instances this is not necessary. A third difficulty is that of treating the cervical adenopathy and the primary lesion at the same time. When the adenopathy is high, it is wiser to include the primary lesion and the adenopathy in the same field which nevertheless should be as small as possible. In this way the deep cervical nodes which lie just behind and lateral to the nasopharynx will also be irradiated. In some instances however, when the nasopharyngeal tumor is an anterior one and the cervical metastasis is somewhat distant, a separate field may be more convenient. Treatment under these conditions is necessarily



Fig. 2-3.—Sketch of a roentgenogram of the base of the skull in a patient with carcinoma of the nasopharynx showing decalcification of the petrosphenoidal portion and enlargement of the foramen lacerum to include the foramen ovale.

protracted, lasting several weeks. The total amount of radiations given will depend, of course, on the individual case but it usually implies a maximum of irradiation compatible with the recovery of the skin after production of moist radioepidermitis of the face and neck, particularly at the level of nodes.

A rapid regression of symptoms usually accompanies the first administrations of radiotherapy. The hypoacusia may disappear but it also may remain present to the end of the treatment because of added edema. Cranial nerve paralysis of the petrosphenoidal group may also regress and vanish. The same is not true, however, of the paralysis due to compression of the retroparotidian group of nerves which will persist in spite of the sterilization of the tumor. Pain is usually relieved after a few weeks of treatment, but,

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## CANCER OF THE OROPHARYNX

The oropharynx extends between two horizontal planes, one passing through the soft palate when in a horizontal position and the other passing at the level of the hyoid bone (Fig 254). This region includes the lower surface of the soft palate, the palatine tonsil, the lingual tonsil, the base of the tongue, the free border of the epiglottis, and the part of the pharyngeal walls included between its limits (Fig 255).

sarcomas The prognosis of lymphoepitheliomas is clouded by their ability to give distant metastases Ilenz obtained six five year survivals in a group of seventeen patients with lymphoepitheliomas The most unfavorable cases are the differentiated carcinomas In thirty patients with carcinoma of the nasopharynx reported by Baclesse, only four survived four years

Nielsen reported the five year end results in patients treated at the Roentgen Station of Copenhagen Of ten patients with lymphosarcomas, three were living, of fifteen with lymphoepitheliomas, four were living, and of eleven with epidermoid carcinomas, four were living

The presence of cranial nerve paralysis is an unfavorable sign but does not necessarily make the case hopeless Actual decalcification of the bones of the base of the skull is an almost certain fatal sign, but in all cases radiotherapy contributes a considerable amount of palliation and prolongation of life even when the disease is not permanently controlled

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A variety of tumors may develop within the oropharynx, each offering different diagnostic, pathologic, therapeutic, and prognostic problems. The following subdivision will be adopted: (1) carcinoma of the soft palate, (2) cancer of the palatine tonsil (carcinomas, lymphoepitheliomas, lymphosarcomas), (3) cancer of the base of the tongue (carcinomas, lymphoepitheliomas, lymphosarcomas), (4) carcinoma of the periepiglottic area (this group includes carcinoma of the glossopharyngeal sulcus, glossoepiglottic fossa, free portion of the epiglottis, pharyngoepiglottic fold, and oropharyngeal wall)

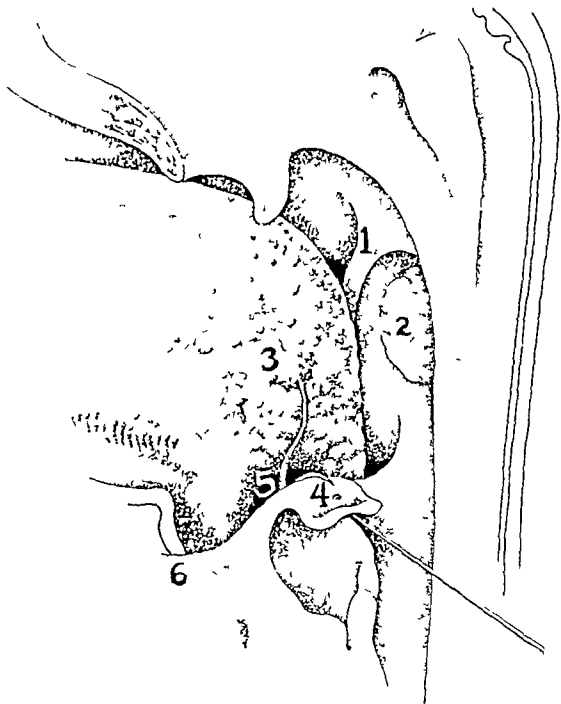


Fig. 255—A posterolateral view of the oropharynx showing 1, anterior pillar of soft palate; 2, tonsil; 3, base of the tongue; 4, free portion of epiglottis; 5, valleculae; and 6, pharyngoepiglottic fold.

## CARCINOMA OF THE SOFT PALATE

### Anatomy

The soft palate or velum is a muscular structure strongly attached to the posterior border of the hard palate. From this point of attachment, it extends first horizontally and then downward to form the uvula in the midline. The two anterior pillars of the soft palate originate at the base of the uvula and find their insertion near lateral aspects of the base of the tongue. These two pillars form an elongated arcade interrupted only in the midline by the uvula. Also from the base of the uvula spring the posterior pillars which follow a

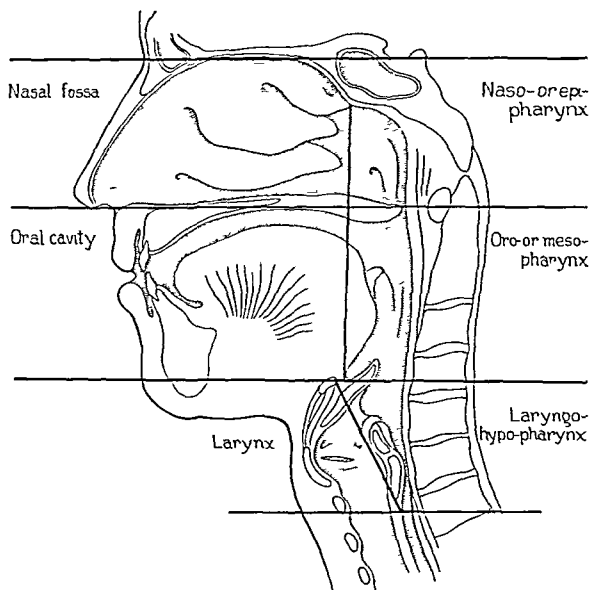


Fig 234—Schematic representation of anatomic subdivisions of the upper air passages



posterior and downward direction and insert themselves on the lateral wall of the pharynx. Between these two pillars there is on each side an excavation, the tonsillar fossa, which is normally occupied by the palatine tonsil.

The mucous membrane which covers the lower aspects of the soft palate is a continuation of the mucous membrane of the mouth and it has a stratified squamous character. In the region adjacent to the hard palate there is a group of independent glandular aggregates, about one hundred in number, producing mostly mucus. They are found in front of the palatine fascia. About twelve more of these glands are found in the uvula (Fig. 220).

**Lymphatics**—The lymphatics of the soft palate are relatively rich, particularly at the midline. They all converge toward a group of nodes found below the anterior belly of the digastric immediately in front of the jugular chain (Fig. 256).

### Incidence

Carcinomas of the soft palate are most often found in men between 40 and 60 years of age. They are very rare in women.

### Pathology

**Gross Pathology**—Carcinomas in this area are usually found on the anterior pillar or on the supratonsillar fossa. They rarely arise from the posterior pillar of the soft palate. The majority of these lesions are ulcerated and

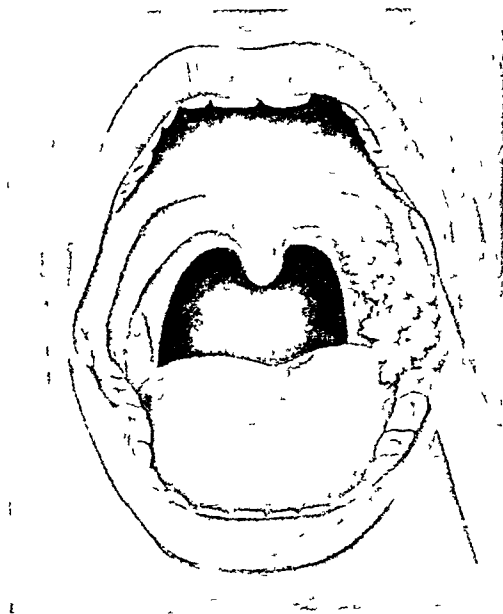


Fig. 257—Papillary epidermoid carcinoma of the anterior pillar of the soft palate extending over the base of the tongue and the buccal mucosa.

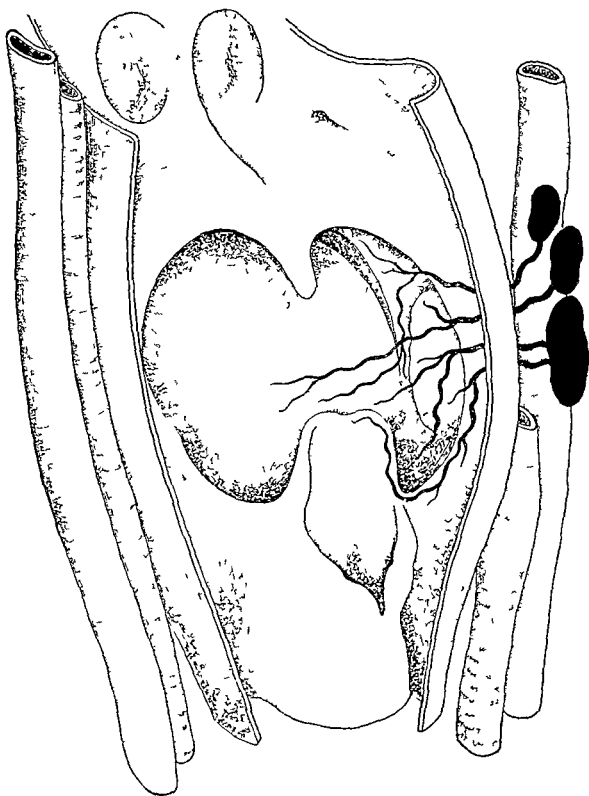


Fig. 2.6—Schematic representation of lymphatics of the oropharynx leading to sublingual group of lymph nodes

posterior and downward direction and insert themselves on the lateral wall of the pharynx. Between these two pillars there is on each side an excavation, the tonsillar fossa, which is normally occupied by the palatine tonsil.

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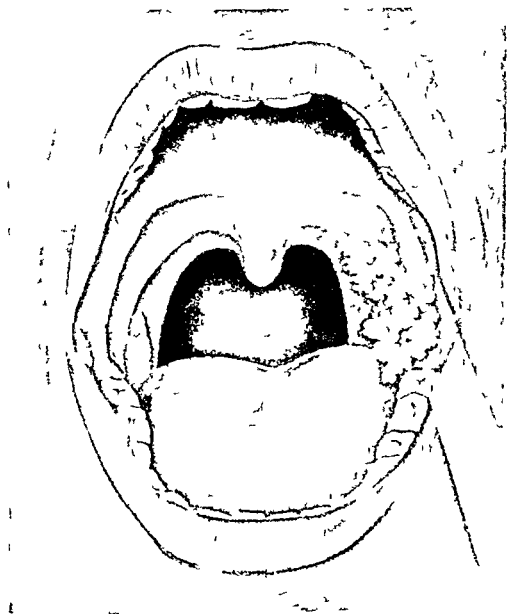


Fig. 257—Papillary epidermoid carcinoma of the anterior pillar of the soft palate extending over the base of the tongue and the buccal mucosa.

diffusely infiltrating. A very small number of lesions which usually develop on the anterior pillar may be papillary in character (Fig 257). Extension toward the buccal mucosa and toward the hard palate is common. Deep extension into the pterygoid fossa is not infrequent.

A small number of cases of carcinoma of the soft palate will present an adenopathy. When this is present, it is represented by a small node located in the upper cervical region.

**Microscopic Pathology**—Carcinomas of the soft palate are epidermoid in type and usually well differentiated. A few cases, however, will show little tendency to differentiation. Adenocarcinomas, which are described as developing in this region, are invariably tumors of salivary gland origin.

### Clinical Evolution

The first symptom of carcinoma of the soft palate is *odynophagia* rapidly followed by *local pain* which radiates to the entire side of the face and head. Pain is an important symptom of these tumors. *Dysphagia* may become very marked. *Trismus* may be present in apparently early lesions betraying the deep infiltration which usually accompanies these tumors. *Bleeding* is not frequent but is sometimes present.

An adenopathy will not be found at the time of examination in the majority of cases. When it appears it is a discrete barely palpable upper cervical node located just below the angle of the mandible. This is usually a hard node showing a very slow growth. Later shotty nodes might be felt in other areas of the neck.

Left to itself carcinoma of the soft palate develops slowly, but the general condition of the patient rapidly deteriorates. The necessity for the administration of strong sedatives and the marked dysphagia contribute to further impoverish the general condition. Most patients with carcinoma of the soft palate whether treated or untreated die with the disease confined to the soft palate and cervical region.

### Diagnosis

In examining these patients an effort should always be made to dissociate those carcinomas arising in the soft palate proper and those which arising in the tonsil, extend to the soft palate secondarily. This is not always possible.

Carcinomas of the soft palate will show a superficial necrotic ulceration with retraction and immobility of the surrounding area of the soft palate. Digital palpation will reveal a diffuse induration well beyond the ulceration. A specimen for biopsy can be secured only by means of a cutting instrument.

Next to the hard palate the soft palate is the most frequent site of development of mucous and salivary gland tumors. These are nonulcerated, slowly growing submucous tumors mostly benign but sometimes malignant, which develop near the anterior surface of the palate in front of the palatine aponeurosis and seldom occur in the midline (Fig 258). They are usually well encapsulated and can be easily excised. Their histology is characteristic (see Tumors of the Hard Palate page 306).

### Treatment

Most carcinomas of the soft palate are, as a rule, markedly differentiated, develop slowly, show little radiosensitivity, and have characteristics which seem appropriate for surgical excision. Surgical excision, however, of carcinomas of the soft palate is usually unsatisfactory. It is difficult to excise the lesion without cutting through tumor, the exact limits of which are difficult to ascertain. Moreover, the resulting deformity of large excisions interferes considerably with deglutition and cannot be well remedied by plastic surgery.



Fig. 258.—Benign tumor of mucous and salivary gland type developing on the left side of the soft palate. The lesion was well encapsulated and easily excised.

Roentgentherapy, although contributing considerable subjective relief and objective improvement, rarely succeeds in sterilizing these well-rooted tumors. The addition of perioral irradiation after external irradiation is probably well indicated, but because of the pathologic features of the tumor, these combined efforts are only rarely successful. Excessive irradiation given in an effort to sterilize the carcinomas of the soft palate usually leads to extensive necrosis, in the borders of which the tumor will often recur.

### Prognosis

The exact curability of carcinomas of the soft palate is difficult to ascertain from the literature, for these tumors are usually reported in the same group with tumors of the tonsil or of the hard palate. The curability, however, is very low. Exceptional cases of papillary growths with only superficial spread and no deep infiltration may be cured by roentgentherapy.

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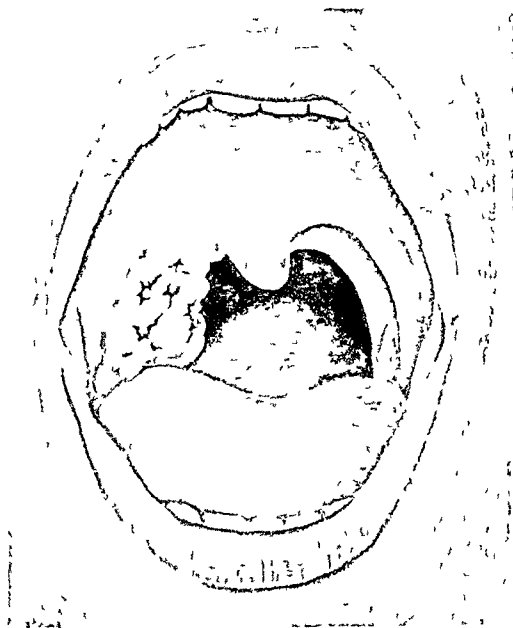


Fig. 259 —Epidermoid carcinoma of the tonsil with beginning extension to the soft palate. These tumors are generally exophytic and show little tendency to infiltrate in depth.

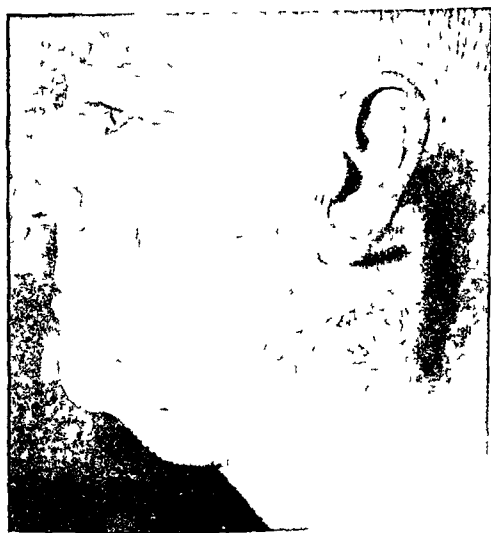


Fig. 260 —Voluminous metastatic adenopathy of the upper cervical and submaxillary region in a case of carcinoma of the tonsil.

## CANCER OF THE TONSIL

### Anatomy

The palatine tonsils are two lymphoid organs situated on each lateral wall of the pharynx between the anterior and posterior pillars of the soft palate. Externally the tonsils are in relation with the lateral wall of the pharynx and, beyond this, with the maxillopharyngeal space.

Each tonsil is covered by a closely adherent capsule which sends deep prolongations into the lymphoid tissue. The tonsils are lined by a stratified squamous epithelium, a continuation of the surrounding mucous membrane but at the level of the tonsillar crypts the mucous membrane takes a pseudo reticular aspect and is infiltrated by numerous lymphocytes.

The lymphatics of the tonsils are rather rich. They gather in four or six trunks which after passing through the lateral wall of the pharynx end in the subdiaphragmatic nodes which lie anterior to the jugular chain (Fig. 256).

### Incidence

Cancer of the tonsil is the second most common form of cancer of the upper air passages superseded only by carcinomas of the laryngopharynx. It accounts for 15 to 30 per cent of all forms of cancer.

Carcinomas of the tonsil are more frequently found in men in their fifth decade of life. Only about 10 per cent occur in women. One third of lymphoepitheliomas and lymphosarcomas, however, are found in women. Lymphosarcomas are found in patients in the third and fourth decades of life more often than are carcinomas.

### Pathology

#### Gross Pathology —

**Carcinomas** — Carcinomas of the tonsil usually arise near the upper pole and are commonly exophytic superficially ulcerated tumors (Fig. 259). Their spread to the soft palate often occurs at the level of the supratonsillar fossa or toward the anterior pillar. This spread is usually superficial and rapidly disappears in the first days of radiotherapeutic treatment. Invasion of the posterior pillar is rarely observed but extension to the glossopharyngeal sulcus is common. An upper cervical metastatic node is almost always present (Fig. 260) and through progressive lymphatic permeation other nodes may appear in the lower cervical region axilla and mediastinum. Blood borne distant metastases are not as common as in carcinomas of the laryngopharynx.

**Lymphoepitheliomas** — Lymphoepitheliomas of the tonsil are usually smooth mostly submucous somewhat lobulated tumors presenting either minimal or no visible ulceration (Fig. 261). They do not infiltrate deeply and their spread is superficial. In advanced cases they may become superficially ulcerated throughout. The impression given is a different one. A large upper cervical adenopathy sometimes bilateral is a constant finding and successive permeation of lymph nodes of the neck and mediastinum occurs faster than in carcinomas. In advanced cases where the treatment has failed metastases to the lungs



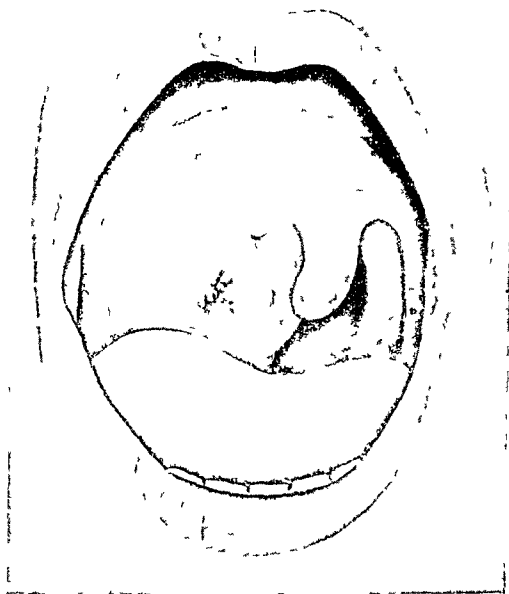


Fig 262—Lymphosarcoma of the tonsil. The tumor is usually smooth shiny and almost spherical in shape due to submucous extension. An ulceration occurs only after trauma.



Fig 263—Same patient as in Fig 262 presenting a voluminous upper cervical node just below and behind the angle of the mandible.

liver, and bones are almost the rule, differing in this from epidermoid carcinomas and lymphosarcomas

**Lymphosarcomas**—Lymphosarcomas of the tonsil develop submucosally and may attain large proportions without presenting an ulceration. The surface of the tumor is covered by the same mucous membrane as the soft palate (Fig 262). Trauma, therapeutic incisions, or biopsy may cause secondary infection which, at times, results in an extensive necrosis of the tumor area. At times a lymphosarcoma may be superficially ulcerated in its early development and extend superficially beyond the midline in a horseshoe fashion. Some lymphosarcomas of the tonsil are rather small and appear grossly as a purely inflammatory tonsil.

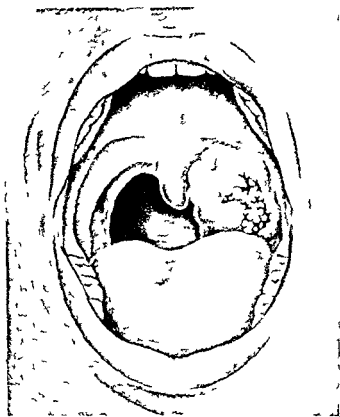


Fig 261—Lymphoepithelioma of the tonsil presenting a polypoid polypoid appearance and only a limited ulceration

A large cervical adenopathy often bilateral is the most common finding in lymphosarcomas of the tonsil (Fig 263) but those cases which develop without ulceration and may occupy the entire oropharynx are usually accompanied by a rather discrete upper cervical adenopathy in the early period of their development. Patients with advanced lesions or lesions which fail to be controlled by treatment die with generalization of the disease which will always include invasion of the retroperitoneal nodes.

#### Microscopic Pathology—

**Carcinoma**—Carcinomas are the most common of tonsillar tumors. Of these a great proportion are rather undifferentiated squamous cell carcinomas. Martin

adenopathy is rapid growing and usually fixed but not adherent to the skin. Subsequent metastatic nodes in the neck appear only in advanced cases. Other lymphatic areas, such as the axilla and mediastinum, appear to be invaded by successive lymphatic invasion.

*Lymphoepitheliomas*—It is characteristic of these tumors that the primary lesion may be so discrete as to pass unnoticed. The fact that they are seldom widely ulcerated and that they do not infiltrate in depth accounts for the lack of symptoms given by the primary lesion. The first symptom is very often the development of a rapidly growing adenopathy. These are found in the upper cervical region behind the angle of the mandible and are usually soft with no tendency to fixation and most commonly accompanied by smaller nodes in adjacent areas. In advanced cases the production of distant metastases to lymph nodes and the lungs, liver, and bone are not exceptional.

*Lymphosarcoma*—Lymphosarcomas of the tonsil have varied forms of clinical onset worthy of consideration. Lymphosarcomas of the tonsil may be divided into three clinical groups according to their mode of onset (Regato). The first group (obstructive) is characterized by the rapid growth of a non-ulcerated, tonsillar tumefaction which may acquire huge dimensions and interfere considerably with deglutition and respiration. There may be no adenopathy or only a rather discrete node palpable in the angulomandibular region. The second group (inflammatory) is characterized by a history of repeated inflammatory-like attacks of pharyngitis accompanied by fever. An upper cervical adenopathy may appear during this acute stage but will show intermittent spontaneous regression without ever entirely disappearing. The diagnosis can be made only by continued observation of the patient and by biopsy. The third group (early metastasizing) is considerably the more commonly encountered. In these cases the lesion of the tonsil is silent and consequently often overlooked. It may be represented by a small focus of tumor within the tonsil or by a pedunculated tumor hidden in the glossoepiglottic fossa. Metastatic nodes first appear in the cervical region on the same side as the primary lesion and are promptly succeeded by other nodes in the axilla and mediastinum. The tumor may rapidly become widespread and for this reason many patients may have an initial examination when the disease has become generalized. In these generalized cases, the poor general condition of the patient, the symptoms of mediastinal enlargement, etc., are predominant in the clinical picture and a diagnosis of primary point of origin in the tonsil may not be established. Lymphosarcomas arising in the nasal fossa, nasopharynx, and base of the tongue may have a similar history. In the presence of such a generalized condition, it may also be difficult or even impossible to establish a definite diagnosis. Without indulging in an academic discussion, we would like to emphasize that primary lymphosarcomas of the tonsil as well as those arising in other areas of Waldeyer's ring do reach this generalized state after rapid progressive extension to distant lymphatic areas. It is worthy of notice that even in such generalized cases bone metastases are rare and that in general only the lymphatic system seems to be thoroughly invaded. Some cases of generalized lymphosarcoma, particularly in children, may send into the circu-

reported only four squamous cell carcinomas, Grade I, of a group of ninety four squamous cell carcinomas. The great majority of cases present a slight differentiation with little or no keratinization. A good number among these carcinomas will show no keratinization at all and will be included in what is usually called transitional cell carcinomas. It is open to question whether some of the so called transitional cell carcinomas are not lymphoepitheliomas which do not appear typical microscopically.

The embryonal character of most of these carcinomas accounts for their insidious development, lack of infiltration, development of metastases, and great radiosensitivity and radiocurability.

*Lymphoepitheliomas*—As described by Regaud, this form of tumor is characterized by cords of clear epithelial cells infiltrated by numerous lymphocytes (Fig 240). This morphologic distinction corresponds to a definite clinical group which is quite distinct from lymphosarcomas and squamous cell carcinomas. The fact that they metastasize to the lungs, liver, and bones and that they carry to these organs their distinctive histologic features and lymphocytic infiltration is argument enough to establish their identity. The fact that they cannot always be identified microscopically and that they may be diagnosed as transitional cell carcinomas or undifferentiated squamous cell carcinomas is only proof of the fact that some pathologic entities do not always have a typical morphologic appearance.

*Lymphosarcomas*—Lymphosarcomas are usually subdivided into several groups according to the character of their cells and stroma. These groups do not correspond to any clinical entity and they do not have any therapeutic or prognostic value but are only of interest to the pathologist.

It must be said that the microscopic diagnosis of lymphosarcoma is not always easy and this is particularly true when the specimen comes from a lymph node. In cases where the primary lesion has not been identified in the upper air passages the pathologist will need the help of the clinician and of further laboratory investigations in order to make a differential diagnosis with other lymphomas.

### Clinical Evolution

*Carcinomas*—A mild pharyngeal discomfort or sensation of foreign body accompanied or followed by slight odynophagia is usually the first symptom in carcinoma of the tonsil. This symptom is so trivial that the patient may delay considerably his consultation with a physician. Pain is infrequently present except in advanced cases. Otalgia on the same side as the lesion and dysphagia appear in moderately advanced cases.

Examination will reveal an enlarged, irregular tonsil usually presenting an ulcerated area in its center. This area may be found indurated but seldom is fixed. When the tumor has spread outside the tonsil, there will be a superficial nodularity of the anterior pillar or supratonsillar fossa in general not ulcerated.

An enlarged lymph node will almost invariably be present in the upper cervical region behind the angle of the mandible. Its appearance may have preceded or accompanied the symptoms given by the primary lesion. This

ably painless but they result in a complete destruction of the tooth regardless of the good condition of this tooth at the time of irradiation (Fig 264). The remaining roots and the open socket are ideal portals of entry to infection. These dental lesions are due to qualitative and quantitative changes of the saliva and not to a direct effect of irradiation (Regato). Consequently, nothing can be gained by protection of teeth during the course of treatment. Because of this, it is wiser to extract all teeth in good or bad condition and to await the healing of the gums before radiotherapy is started. The apparent loss in time will be compensated by a diminution of the secondary infection and a greater safety for the treatment so given.

### Prognosis

The prognosis for tumors of the tonsillar region is a relatively favorable one. Coutard reported twenty-one patients (32 per cent) living and well five years or longer in a series of sixty-five unselected patients with carcinomas of the tonsil treated with external irradiation alone. Martin and Sugarbaker reported fifteen five-year survivals in a series of ninety-two patients with carcinoma of the tonsil treated by external roentgentherapy, peroral roentgentherapy, and interstitial irradiation of the nodes. Some cases of failure in treatment are due to underdosage and lack of sterilization of the primary lesion, but in most cases the treatment fails because of subsequent metastases to the neck and generalization of the disease.

The prognosis of lymphoepitheliomas is difficult to establish in view of the small number of cases reported. Although the disease is very radiosensitive and locally curable, it has a tendency to become generalized. Berven reported on thirteen patients with lymphoepithelioma of the tonsil, eight of whom were well five years after the treatment.

Lymphosarcomas of the tonsil have the best prognosis in the group. Roentgentherapy is successful in a rather high percentage of those patients in whom the disease is confined to the limits of the neck. Berven reported seventeen patients (34 per cent) living and well five years after the treatment in a series of forty-nine patients with lymphosarcomas of the tonsil. Regato reported fifteen patients (40 per cent) well and free of disease five years after treatment in a series of thirty-seven patients with lymphosarcomas of the tonsil treated by external roentgentherapy alone. After the treatment of lymphosarcomas, most patients presenting generalization of the disease die within the first year. Those dying in the second and third years usually have successive permeation into adjacent lymphatic areas and die finally of generalization of the disease. The three-year end control statistics of cases of lymphosarcoma do not differ much from the five-year end results.

## CANCER OF THE BASE OF THE TONGUE

### Anatomy

The base of the tongue is the portion of that organ situated behind the sulcus terminalis or lingual V formed by the circumvallate papillae. Laterally

lating blood a large number of neoplastic cells. This usually results in a diagnosis of leukemia. However, by means of supravital staining, hematologists have learned to recognize these neoplastic cells from leucemic cells and have labeled this condition as leucosarcoma (Sternberg-Wiseman).

### Diagnosis

Taking into consideration details of the clinical history and of the gross descriptions given, the pathologic entity of a tumor of the tonsil may be suspected at clinical examination. However, this suspicion should always be confirmed by biopsy. The specimens for microscopic examination are easily removed from this area by means of any grasping forceps.

Aspiration of the metastatic nodes should always be done as a matter of record. Other diagnostic measures such as roentgenograms are seldom of additional value in the diagnosis of extension of the local disease, but they may be very useful in the diagnosis of distant metastases, particularly of the mediastinum. A routine roentgenogram of the chest should always be taken in all cases of lymphosarcoma or lymphoepithelioma.

**Differential Diagnosis**—Tuberculosis of the tonsil and of the soft palate is usually characterized by a superficial grayish ulceration surrounded by confluent areas of false membrane. In general there will also be advanced tuberculosis of the lungs.

Syphilitic gumma of the palatotonsillar region is a rare occurrence. The syphilitic ulceration usually has punched out borders and is not accompanied by induration. Primary tumors of the parotid gland which develop deeply may sometimes produce a deformity of the lateral wall of the oropharynx and a displacement of the tonsillar region, which may be taken for a tumor of this area. These tumors present a very slow development and they do not become ulcerated.

### Treatment

**SURGERY**—Although the tonsil is a very accessible organ, surgical intervention has nothing to offer. Radical operations which imply resection of parts of the mandible have been abandoned because of the high operative mortality and the poor results. Tumors arising in this area with the exception of very differentiated carcinomas, present pathologic features unfavorable to surgical excision and auspicious for treatment by radiations. Moreover, these tumors are usually accompanied by large cervical adenopathies so that the principal problem is not the control of the primary lesion.

Surgical treatment of the metastatic cervical nodes after the primary lesion has been controlled is not indicated for several reasons. In the first place metastatic carcinoma from a tonsillar primary lesion is usually highly placed in the neck where complete excision is troublesome. Then, too, in the overwhelming majority of cases these metastatic nodes react favorably to radiotherapy.

**ROENTGENTHERAPY**—Roentgentherapy is the best treatment for cancer of the tonsil and its corresponding adenopathy. The treatment should be protracted over a period of five to six weeks. This will eliminate the general



FIG. 2-5—Epithelioma carcinoma of the base of the tongue presenting a fissured ulcer and deep diffuse infiltration.

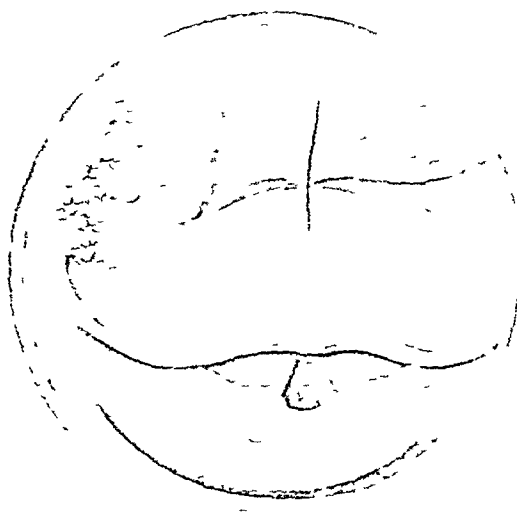


FIG. 2 —Carcinoma of the glossoephiaryngeal space.

the base of the tongue extends to form the glossopharyngeal sulcus which lies between the base of the tongue and the lateral wall of the pharynx. Posteriorly the base of the tongue ends in forming the anterior wall of the glossopygillotic fossae or valleculae. A fold that is situated in the midline and extends from the base of the tongue to the free border of the epiglottis separates the valleculae.

The base of the tongue lacks most of the different papillae which cover the anterior two thirds of the tongue, but it is richer in neurogenic elements of the sense of taste or taste buds. The mucous membrane of the base of the tongue is a stratified squamous epithelium covering numerous tubercles or encapsulated lymphoid nodules which give an irregular appearance to its surface. This mucous membrane is not as firmly adherent to the underlying muscle at the base of the tongue as it is on the anterior two thirds.

**Lymphatics**—The lymphatic network of the base of the tongue is markedly independent from the rest of the lymphatics of the tongue. The collecting trunks pass through the lateral pharyngeal wall just below the palatine tonsil and in the subdigastric group of nodes which drain most of the lymphatics of the oropharynx (Fig 256).

### Incidence and Etiology

Cancer of the base of the tongue is not as frequent as cancer of its mobile portion. The overwhelming majority of cases of carcinoma of the base of the tongue are men in their sixth decade of life. About one third of the lymphoepitheliomas and lymphosarcomas, however, are found in women. Khanolkar reported a series of 1 000 carcinomas of the tongue observed at the Tata Memorial Hospital of Bombay, India. The majority of these developed on the base of the tongue. This is in contradiction to the greater incidence of carcinoma of the mobile portion of the tongue in most other countries. It is possible that many among the cases reported by Khanolkar could be classified as carcinoma of the glossopharyngeal sulcus, but at any rate this represents an incidence of carcinoma in this region which is considerably out of proportion. This has been attributed to the common habit among some oriental races of betel nut chewing. In the light of the fact that carcinoma of the oral cavity seems to be equally prevalent in some regions where the betel nut chewing is not a common habit this argument is open for further clarification (Khanolkar).

### Pathology

**Gross Pathology**—Most of the malignant tumors of the base of the tongue are carcinomas, lymphoepitheliomas (and transitional cell carcinomas), and lymphosarcomas. Very rarely other tumors are found such as connective tissue sarcomas and tumors of salivary gland origin (see Tumors of the Salivary Glands page 618).

**Carcinomas**—Epidermoid carcinoma of the base of the tongue is one of the most infiltrating types of cancer of the upper air passages. The tumors seldom affect the outside dimensions of the base of the tongue but they infiltrate deeply into the muscles. Fissurelike ulcerations may be found on either



side of the base of the tongue and are often in the midline (Fig 265). These ulcerations are surrounded by diffusely disseminated tumor. In 225 cases of carcinoma of the base of the tongue reported by Roux-Berger, ninety-seven extended on both sides of the midline, only 128 lesions were strictly unilateral.

Metastatic adenopathies are found in the upper cervical regions. They are usually discrete and often bilateral. Roux-Berger, in his 225 cases, reported a 63 per cent incidence of bilateral adenopathies in those cases where the primary lesion extended beyond the midline, and 34 per cent of bilateral adenopathies in those cases in which the primary lesion appeared clinically confined to one side. Only eighteen of the 225 cases were without cervical adenopathy. Distant metastases are extremely rare. Death occurs because of failure to control the primary lesion, hemorrhage, or deterioration of the general condition with intercurrent complications. Seldom are distant metastases observed.

Carcinomas of the base of the tongue are not to be confused with carcinomas arising on the glossopharyngeal sulcus, which always invade the tongue secondarily but rather superficially (see Carcinomas of the Periepiglotte Region, page 378).

*Lymphoepitheliomas (and Transitional-Cell Carcinomas)*—These are usually nonulcerated, polypoid, unilateral tumors (Fig 267). Metastatic nodes are found in the upper cervical region, they are usually voluminous. Spread of the disease to other lymphatic areas, lungs, and liver is frequently found in generalized cases.

*Lymphosarcomas*—Lymphosarcomas of the base of the tongue arise from the multiple submucous lymphoid nodules of this organ and are usually bilateral and nonulcerated. They may rapidly fill the entire distance between the base and the posterior wall of the tongue (Fig 268). An adenopathy is almost always found on one and often on both sides of the neck. Rapid spread of the disease to other lymphatic areas of the neck, axilla, mediastinum, and retroperitoneal regions follows the same course as other primary lymphosarcomas of the upper air passages.

**Microscopic Pathology**—Unlike carcinomas of the tonsil, epidermoid carcinomas which develop in the base of the tongue are usually well differentiated. Lymphoepitheliomas and lymphosarcomas have the same character as those found in other areas (see Cancer of the Nasopharynx and Cancer of the Tonsil, pages 333 and 364).

### Clinical Evolution

*Carcinomas*—The onset of these tumors is usually accompanied by diffuse pain which may become rapidly marked. *Odynophagia* and *dysphagia* usually accompany this pain and contribute to a rapid deterioration of the general physical condition. Difficulty in protrusion of the tongue will interfere with speech, making it unintelligible. Hemorrhages may appear in the advanced stages.



Fig 217 —Lymphoepithelioma of the base of the tongue presenting a polypoid appearance and visible ulceration

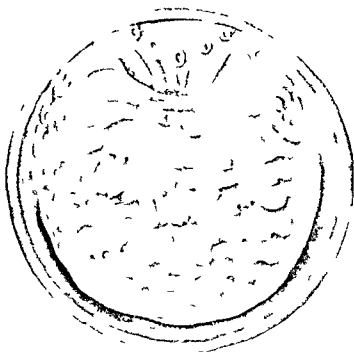


Fig 268 —Lymphosarcoma of the base of the tongue coming in contact with the posterior pharyngeal wall and covering the larynx. Usually there is no ulceration or rarely a superficial one due to trauma

will abolish any question of a differential diagnosis with myosarcomas, tumors of salivary gland origin, and other rare forms of cancer of the base of the tongue. An aspiration biopsy of the metastatic nodes should always be done.

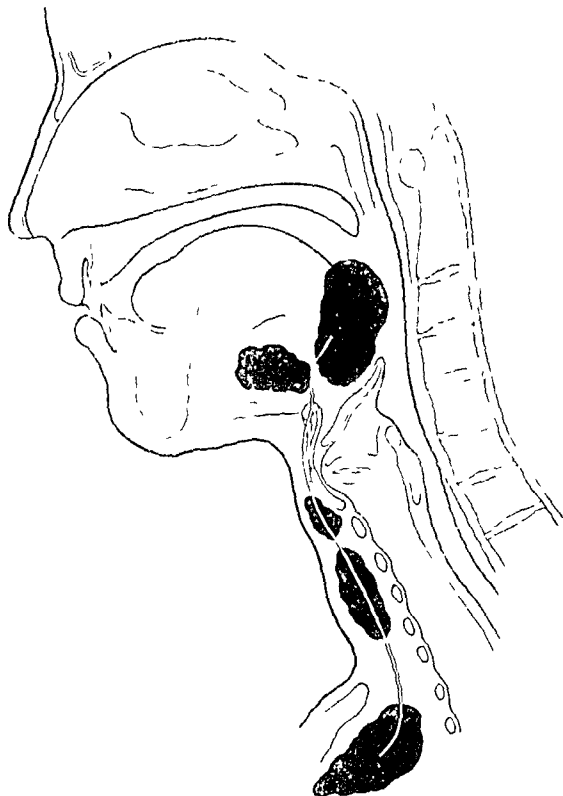


Fig. 269.—Thyroglossal cysts may be found at the base of the tongue or on the anterior midline of the neck.

### Treatment

**SURGERY**—Surgical treatment of tumors of the base of the tongue is well justified through an oral approach in benign lesions such as lingual thyroids or benign salivary tumors, but in the treatment of malignant tumors, the oral approach is not satisfactory. Larger operations such as lateral pharyngotomy or transhyoid pharyngotomy would seem justified in the treatment of epidermoid carcinomas, because of the almost constant failure of radiotherapy in such infiltrating tumors. But these radical surgical procedures invariably fail to cure. In the treatment of lymphoepitheliomas and lymphosarcomas, highly radiosensitive and radioemable tumors, such operations are hardly justified.

Neck dissections for the metastatic nodes from epidermoid carcinomas of the base of the tongue are well indicated. It is, however, obligatory for the

An adenopathy is usually found in the upper cervical region. The nodes, however, are often small and nontender and remain stationary over a long period of time. Metastatic nodes are often bilateral.

*Lymphoepitheliomas*—The onset of lymphoepitheliomas of this region is characteristically silent. The first manifestation of the disease may be the appearance of a metastatic adenopathy in the upper cervical region. The primary lesion seldom produces any symptoms and its discovery is usually the result of perspicacity on the part of the examiner. Seldom is there pain, odynophagia, or dysphagia accompanying these tumors.

The adenopathy is usually unilateral, rapid growing, and soft, with little tendency to fixation to the underlying tissues or to the skin. Successive metastases to the lower cervical region, mediastinum, axilla, lungs and liver are not infrequent in uncontrolled cases.

*Lymphosarcomas*—The clinical evolution of lymphosarcoma of the base of the tongue is very much like that of lymphosarcoma of the tonsil. It may develop giving no symptoms until the tumor has become large enough to hinder deglutition and produce mechanical dysphagia and a nasal twang of the voice. The metastatic nodes if present, will be discrete. Contrarily, other forms of lymphosarcoma of the base of the tongue may remain locally unsuspected presenting a very slow growth, while the clinical onset and course are dominated by the development of metastatic adenopathy of the cervical regions or distant lymphatic nodes. When the primary lesion has not been suspected or found, such generalized cases may lead to the diagnosis of primary lymphosarcoma of these nodes.

Lumbar pain and rapid loss of weight are indicative of retroperitoneal metastases and generalization of the disease.

### Diagnosis

*Differential Diagnosis*—A condition worthy of mention in the differential diagnosis of tumors of the base of the tongue is a thyroglossal cyst in this area. This cyst may develop from remnants of the thyroglossal duct anywhere in the anterior midline of the neck and less often under the base of the tongue (Fig 269). It is congenital but is usually found in adult females who present a physiologic enlargement of the cyst during puberty or pregnancy. Enlargement of the cyst has also been noticed after oophorectomy or thyroidectomy. Thyroglossal cysts are characterized by a nonulcerated, slightly lobulated tumor factions usually on the midline of the base of the tongue. The base of the tongue is sometimes the site of origin of salivary and mucous gland tumors. These are very slow growing nonulcerated, painless tumors which may acquire voluminous dimensions (Fig 270) and interfere with deglutition and speech. They may be benign or malignant (see Tumors of Hard Palate page 306) and in general develop so slowly that abstention may be justified in the aged patient.

A clinical impression of carcinoma, lymphoepithelioma or lymphosarcoma of the base of the tongue must always be confirmed by biopsy. The biopsy

**CURIETHERAPY**—Interstitial irradiation by means of radium element needles is rather difficult in epidermoid carcinomas of the base of the tongue, where it might seem indicated. The possibilities of a homogeneous irradiation of this area are almost nil. However, in very small tumors, where the disease is well circumscribed, such a procedure may be possible and successful. In the treatment of lymphoepitheliomas and lymphosarcomas, where external irradiation will suffice to sterilize the primary lesions, interstitial irradiation is not justified.

Interstitial irradiation with radium emanation seeds offers the same disadvantages. Martin advises an implantation of radium seeds through the soft tissues of the anterior midline of the suprahyoid area while their distribution is controlled by a palpating finger placed over the base of the tongue. Such a procedure implies obvious inaccuracies and could be successful only in the radiosensitive types of tumors like lymphoepitheliomas in which its use is not justified.

### Prognosis

The prognosis of epidermoid carcinomas of the base of the tongue is an ominous one. Very few cases are locally cured. Baclesse reported only seven patients remaining well five years in a series of 127 treated by roentgentherapy. The majority of them, however, benefit by considerable transitory palliation when treated by external roentgentherapy.

The curability of lymphosarcomas of the base of the tongue is rather high when the disease is diagnosed before it has spread beyond the limits of the neck. Most cases of failure in the treatment will be due to the presence of unsuspected distant metastases. In an unpublished review on twelve patients with lymphosarcoma of the base of the tongue treated at the Foundation Clinic from 1920 to 1932, four appeared well five years after the treatment (Regato).

## CARCINOMA OF THE PERIEPIGLOTTIC AREA

### Anatomy

The free portion of the epiglottis is that part which is found above the level of the hyoid bone. It is composed of cartilage surrounded by fibroelastic tissue and is covered by a thin mucous membrane. Laterally it is attached to the walls of the pharynx by two fibroelastic membranes, the pharyngoepiglottic fold. Anteriorly, the free portion of the epiglottis and the base of the tongue form the valleculae (or glossoepiglottic fossae) which lie on each side of the glossoepiglottic fold (Fig. 255).

The lateral and posterior walls of the oropharynx extend from the level of a horizontal line passing by the soft palate to the level of another line passing through the hyoid bone.

### Incidence

Carcinomas of the periepiglottic area are seen only half as often as those of the hypopharynx. They are encountered predominantly in men in their fifth and sixth decades of life.

primary lesion to be clinically controlled before the neck dissection is undertaken, and such sterilization of the primary lesion is seldom obtained. In addition, metastatic carcinoma from a primary lesion in the base of the tongue is quite often bilateral, and the undertaking of the double operation with its higher operative mortality will require further assurance that the risk is worth taking. Roux-Berger reported eight patients well five years after operation in a series of forty-two who had radical neck dissections for metastatic epidermoid carcinoma of the base of the tongue. Four of these eight, however, showed no actual metastatic involvement of the nodes.

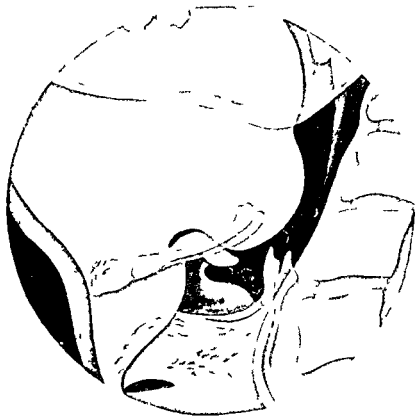


Fig. 770—A sketch of a roentgenogram of the soft tissues of the neck showing a smooth growth on the base of the tongue which has displaced the hyoid and epiglottis downward. The tumor had been growing for many years and was of mucous and salivary gland type.

**ROENTGENTHERAPY**—By general agreement roentgentherapy is the preferred treatment for tumors of the base of the tongue. The best results are obtained by irradiating through two lateral fields protracting treatment from four to six weeks, and following the same principles which have been outlined in the treatment of cancer of the tonsil.

External roentgentherapy is almost always fruitless in the treatment of epidermoid carcinomas but, on the other hand, the control of the primary lesion may be achieved in lymphoepitheliomas, transitional cell carcinomas, and lymphosarcomas. In these the failures of treatment will be due to inadequate irradiation or dosage or to development of the disease outside of the field of action.

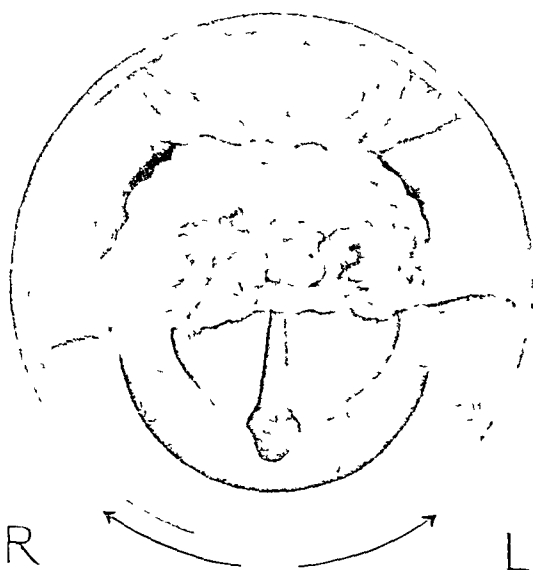


Fig. 272—Carcinoma of the free portion of the epiglottis. These tumors usually show superficial necrosis and although extensive are among the most curable of carcinomas of the pharynx.



Fig. 273—Carcinoma of the right pharyngoepiglottic fold. These are rather rare tumors, usually extensive and consequently rather difficult to identify as to point of departure. The free portion of the epiglottis is curled due to lateral compression.

### Pathology

**Gross Pathology**—Carcinomas of the *glossopharyngeal sulcus* extend superficially both over the surface of the tongue and over the lateral wall of the pharynx and tonsil. They are superficially necrotic and seldom infiltrate to any depth. They are usually accompanied by a unilateral upper cervical adenopathy (Fig 266).

Carcinomas of the *glossoepiglottic fossae* or *valleculae* are noninfiltrating. They grow in the narrow space between the base of the tongue and the epiglottis and usually become deeply excavated (Fig 271). Retention of particles of food in the excavation causes considerable secondary infection and discomfort. Very rarely carcinomas of this area will infiltrate the muscles of the tongue and produce a deep excavation into that organ similar to that of carcinomas of the base of the tongue. Most carcinomas of the *valleculae* are unilateral. An upper cervical adenopathy is usually present on one side and sometimes on both sides.



Fig 271—Carcinoma of the right side of the glossoepiglottic fossa (*vallecula*) with secondary infiltration of the epiglottis and pharyngoepiglottic fold. Notice the edema of the right false cord which may represent tumor extension through the cartilage of the epiglottis.

Carcinomas of the *free portion of the epiglottis* are usually bulky, presenting large areas of spontaneous necrosis and abundant secondary infection. Their infiltration does not often extend beyond the free border of the epiglottis itself, even though this border is usually totally destroyed (Fig 272). The spontaneous necrosis of these tumors creates considerable secondary infection which, in turn, has its repercussions on the general condition of the patient. A voluminous, often bilateral, midcervical adenopathy almost always accompanies these tumors.



### Diagnosis

The diagnosis of carcinomas of the periepiglottic area does not offer great difficulties. The lesions are usually of a typical carcinomatous appearance and the clinical impression may be easily confirmed by biopsy. The removal of specimens for microscopic examination is rather easy in this area.

When a cervical adenopathy is the first symptom, a thorough search for the primary lesion in the epiglottis and other areas of the pharynx and mouth should precede any therapeutic undertaking, for there exists a great number of other conditions, benign and malignant, which may be confused with the metastatic carcinomatous mass of the neck. The diagnosis of these conditions should always be made by exclusion if the search for the primary lesion in the pharynx has been fruitless.



Fig. 271—Sketch of a roentgenogram of the soft tissues of the neck in a case of exophytic tumor of the free portion of the epiglottis. Notice the air spaces between protrusions of tumor mass.

Radiographic examination of the soft tissues of the neck will always be of some additional interest in establishing the limits of extension of a tumor (Fig. 271). This is not always possible on pharyngeal examination.

**Differential Diagnosis.**—*Tuberculous adenitis* may sometimes reproduce a picture of metastatic carcinoma of the neck. If a thorough examination of the pharynx and oral cavity fails to reveal any suspicious area or point of departure, an aspiration of the cervical mass will most often resolve the problem of diagnosis. Tuberculous adenopathies usually contain thick yellow pus,

Carcinomas of the *pharyngoepiglottic fold* expand between the free portion of the epiglottis and the lateral wall. As a consequence, the epiglottis is distorted and the larynx somewhat displaced (Fig 273). These tumors seldom infiltrate. They become bulky, presenting superficial ulcerations, and are attended by a midcervical unilateral adenopathy.

Carcinomas of the *lateral wall* of the oropharynx are seldom confined to the strict anatomic limits of this region. Most of them extend downward to the lateral wall of the hypopharynx and are similar in character to the tumors of the lateral wall of the piriform sinus. They may infiltrate early the lateral wings or superior horns of the thyroid cartilage and sometimes quickly invade the internal carotid artery.

Carcinomas of the *posterior wall* of the oropharynx appear as smooth tumor nodules which grow forward narrowing the anteroposterior diameters of this region. The tumor may come in contact with the soft palate and even the base of the tongue. These are tumors that may finally ulcerate, usually in the midline because of the trauma of ingestion of food. A bilateral adenopathy may or may not be present but if present is usually discrete.

**Microscopic Pathology**—All of the tumors of this area are epidermoid carcinomas with a lesser degree of differentiation in general than the epidermoid carcinomas of the oral cavity.

### Clinical Evolution

Very frequently carcinomas of the periepiglottic area will manifest themselves by a metastatic cervical adenopathy, while the primary lesion has given no symptoms of its presence. In the majority of cases the only symptom given by the primary lesion is merely a slight sore throat or mild *odynophagia*. With advancement of the disease, these symptoms become more marked and *dysphagia* may appear. *Cough* particularly following ingestion of food, is rather frequent. *Hoarseness* is only present in very advanced tumors with accompanying edema of the false cords. *Pain* is a rare symptom.

The general condition of the patient is more rapidly affected than in any other group of tumors of the pharynx or larynx. Because of the dysphagia and secondary infection, the patients may lose considerable weight and appear cachectic.

A rapid growing adenopathy of the mid and upper cervical regions is an almost constant finding and depending on the location of the primary lesion is very often bilateral. These adenopathies are usually rapid growing and may require large dimensions. They form a bulky mass made up of conglomerate matted nodes and smaller nodes which may be found in the direction of the anterior cervical chain.

In the majority of cases of carcinomas of the periepiglottic area, the adenopathy may appear before the primary lesion has given any symptoms.

Distant metastases to the mediastinum, lungs and abdominal viscera are not infrequently found in cases which come to autopsy. The percentage is among the highest for tumors of the upper air passages.

the cervical region. The appearance of a left supraclavicular mass is typical of some tumors of the abdominal cavity and pelvis. It may be found to proceed from adenocarcinomas of the stomach or epidermoid carcinomas of the cervix and although it is more frequent in advanced cases, it may sometimes be the first clinical manifestation of the disease (sentinel node, Virchow's, Troisier's).

A primary diagnosis of *branchiogenic carcinoma* or carcinoma developing at the expense of the embryonic remnants of the branchial clefts should always be taken with doubt. The overwhelming majority of such cases which have been reported in the past are actually metastatic carcinomas from unsuspected pharyngeal lesions. If branchiogenic carcinomas exist, they are an extreme rarity.

*Carotid body tumors* are most commonly found in individuals 40 to 60 years of age and do not predominate in either sex. The tumor develops on the superior anterior cervical triangle of the neck at the level of the bifurcation of the common carotid artery with which the tumor is intimately associated. The tumors may cause pressure on the esophagus, larynx, vagus nerve, or superior cervical ganglion and be the cause of dysphagia, dysphonia, etc. They develop slowly and may rarely metastasize to regional nodes. Pathologic study will reveal a connective tissue capsule which divides the tumor into lobules. These cells have a pale epithelial appearance with a somewhat granular protoplasm. The nuclei are eccentric and contain chromatin. The cells usually contain granules having an affinity for chrome salts, which causes them to stain brown. These tumors may rarely be bilateral (Phelps). The treatment of choice is a surgical excision. In about 50 per cent of the cases (Harrington), this will necessitate a ligation of the carotid artery, which may have fatal consequences. Carotid body tumors which develop in the upper cervical region near the division of the common carotid are rare but have a typical histologic appearance. They usually have a long history of a slow growth. The diagnosis may be established by biopsy.

To summarize the diagnosis of cervical tumors, careful consideration should be given to the history, length of evolution, consistency, position of the mass, and the presence of symptoms or physical findings elsewhere in the body. Although an aspiration biopsy may not offer a definite diagnosis, it is of great value and should always precede the decision of obtaining a larger specimen through incision. The diagnosis of epidermoid carcinoma, lymphosarcoma, or lymphoepithelioma of a metastatic mass of the neck should lead to the suspicion that a primary lesion exists in the upper air passages.

### Treatment

**RONTGEN THERAPY**—Because of their location, high degree of radiosensitivity, and the almost constant presence of cervical adenopathy, carcinomas of the periepiglottic area are recognized to be under the domain of radiotherapy.

External roentgentherapy is complicated by the necessity of irradiating a voluminous cervical mass in addition to the primary lesion. Thus, of course

while metastatic adenopathies are most often solid. Aspiration of caseous material or clear fluid is, however, compatible with a metastatic carcinomatous lesion.

A *symphilitic adenopathy* of the neck is usually a disseminated moderate enlargement of many nodes, and they never attain great volume. An inflammatory cervical adenopathy may or may not be bilateral. The nodes are, as a rule, tender and accompany some inflammatory condition of the oral cavity or pharynx. It should not be forgotten, however, that some forms of lymphosarcoma have a pseudoinflammatory clinical behavior. Inflammatory conditions are considerably more frequent in younger individuals in whom carcinomatous lesions are unusual. No clinical diagnosis of inflammatory adenopathy should be made, however, even in young individuals without a thorough examination of the nasopharynx where an early lesion may be hidden.

*Branchiogenic cysts* of the neck may sometimes be confused with a metastatic adenopathy. These usually appear in the upper cervical region just below the angle of the mandible and may become very large. Their thick wall may be an obstacle to the establishment of their cystic nature on clinical examination. Aspiration of a clear fluid will bring about a collapse of the tumefaction. These branchiogenic cysts are more frequently found in young individuals.

*Thyroglossal cysts* occur along the anterior midline of the neck and consequently are seldom the cause of confusion in the differential diagnosis with a metastatic adenopathy. *Dermoid cysts* of the neck are more often found in early life and are less frequent in the neck than elsewhere. The cysts contain well developed structures (hair, nails, teeth) and may show calcification on radiographic examination. In the presence of a solid mass of the neck, an aspiration biopsy may be a very helpful procedure which implies no untoward effects. If a tentative diagnosis of malignant lymphoma is established, usually an excision of one of the smaller nodes is preferable for histologic study. In the presence of a lymphomatous mass of the neck, a primary lesion of the upper air passages in the base of the tongue, tonsil, nasal fossa, or nasopharynx should be looked for. These primary lesions are usually silent and are sometimes discovered only at autopsy. In Hodgkin's disease the nodes have a tendency to develop on the anterior lower part of the neck. The masses are polylobated and the matted nodes conserve some of their individuality. There is usually considerable periadenitis. The removal of one of the smaller nodes will confirm the diagnosis. The leucemic masses of the neck may offer difficulties with the diagnosis in the group of lymphomas. In such cases a bone marrow biopsy, a blood count, a basal metabolic rate, and the condition of the spleen will add information of value in the diagnosis.

When aspiration biopsy has given a positive diagnosis of carcinoma and no primary lesion has been found in the upper air passages, other points of origin should be considered. Carcinoma of the thyroid may give metastases along the anterior cervical chain while a primary lesion in the thyroid is not even palpable. Such metastatic carcinomas of the thyroid are often labeled erroneously as aberrant thyroids. Carcinomas of the lung may metastasize to

of failure of the treatment is not the inability to sterilize the primary lesion, but the difficulty of sterilizing oversized, secondarily infected metastasis and the spread of the tumor to neighboring areas. Some of the cases which are cured locally may die within the first three years as a consequence of development of distant metastases. Baclesse reported on 102 patients with epidermoid carcinoma of the vallecula and free portion of the epiglottis treated in Coutard's service from 1920 to 1938, sixteen of whom were living and well after five years.

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requires rather large fields of irradiation. In order to facilitate the irradiation through moderately large fields without untoward effect on the general condition of the patient the daily dose should be kept at a low level. It is fortunate, therefore, that the majority of these tumors do not require a large daily dose. This protraction will diminish the intensity of the reaction of the skin and mucous membrane and avoid greater deterioration of the patient's general condition. Two lateral fields of irradiation should be used. If the adenopathy is unilateral one of these fields may not need to be very large and be directed to the primary lesion only. On the side of the adenopathy the total dose should attain a higher level to assure the sterilization of the nodes.

As a general rule the patients will develop a dysphagia during the course of the treatment because of a radioepithelitis of the mucous membrane. Such a dysphagia is unavoidable but it may be kept within limits compatible with the ingestion of liquid food. In some rare instances where the patient is unable to swallow, feeding through a nasal tube may be necessary.

**SURGERY**—Surgical treatment of the adenopathy by means of a neck dissection is not an accepted procedure for several reasons: (1) because the histologic characteristics of these tumors are rather undifferentiated, (2) because they are usually bulky and present numerous adhesions, (3) because they are often bilateral, (4) because treatment of the cervical adenopathy should require assurance of sterilization of the primary lesion and this is a recognized radiotherapeutic problem, and (5) because these tumors are highly radiosensitive and simultaneous irradiation with the primary lesion may be done.

**CUPIFILLARY**—Interstitial irradiation of the cervical nodes with radium emanation seeds has been advised. Such a procedure may be a good complement of insufficient external irradiation but in general it has the disadvantages of all forms of interstitial irradiation, namely, the lack of homogeneous distribution of the necessary dose and the inability to include other possible neighboring foci not suspected of involvement at the time of curietherapy.

### Prognosis

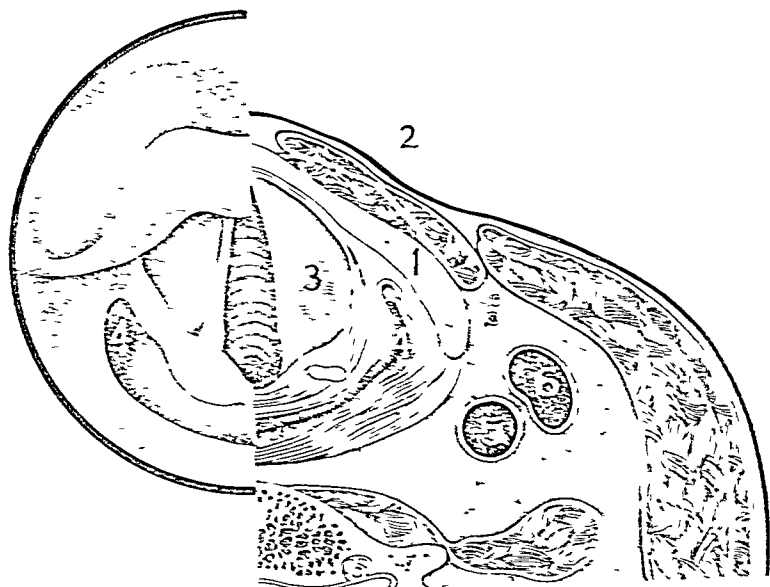
The prognosis of carcinomas of the periepiglottic area as well as that of carcinoma of the glossopharyngeal sulcus and posterior wall of the oropharynx is a very good one. When these tumors become secondarily infected and there is loss of weight and a foul breath the clinical impression is unfavorable. Yet a great number of these tumors do well after roentgentherapy, and they should always be given a chance of receiving a complete treatment.

In the majority of publications available, tumors of the periepiglottic area are included in reports of carcinomas of the hypopharynx. The percentage of results obtained is largely based on the carcinomas of the periepiglottic area. Although there are no available figures to illustrate the favorable prognosis of this group of tumors, it may be said without hesitancy that they have the most favorable prognosis among carcinomas of the pharynx with the exception only of carcinomas of the palatine tonsil. The most frequent cause

of hypopharyngeal tumors are those which arise on the free border of the epiglottis or the pharyngeal fold and which anatomically correspond to the epipharynx.

### Anatomy

The laryngopharynx or hypopharynx surrounds the larynx posteriorly and laterally and extends between two horizontal planes, one of which passes through the aryoid bone and the other through the lower border of the cricoid cartilage. These points correspond to the levels of the third and sixth cervical vertebrae.



This is a schematic representation of the upper part of the pharynx and larynx on the right side. The larynx is shown in the center, with the pharynx extending upwards and backwards. The epiglottis is shown as a small, leaf-like structure at the top. The cricoid cartilage is shown as a ring-like structure below the larynx. The aryoid bone is shown as a small, round structure at the top of the pharynx. The diagram is labeled with numbers 1, 2, and 3. 1 points to the larynx, 2 points to the pharynx, and 3 points to the epiglottis.

The laryngopharynx is formed by two elongated pearlike gullets, the piriform sinuses, which extend on both sides of the larynx posteriorly from the pharyngeal-epiglottic fold to the mouth of the esophagus (Fig 275). Laterally the piriform sinus lies against the inner aspect of the thyroid cartilage. Behind the posterior border of the thyroid cartilage the internal carotid runs very near the lateral wall of the hypopharynx (Fig 276). The medial wall of the piriform sinus is formed by the arytenoepiglottic fold above and by the muscles which form the mouth of the esophagus below. Through this thin layer of muscles the piriform sinus is in very close relationship with the ventricle of the larynx and also with the outer aspect of the cricoid cartilage.

Anteriorly the hypopharynx communicates with the larynx through an encephalic opening the borders of which constitute the limits between the hypo-

# CARCINOMA OF THE LARYNGOPHARYNX (HYPOPHARYNX)

With the exception of tumors arising on the posterior wall of the hypopharynx, most carcinomas of this region sooner or later invade the larynx. For this reason they have often been erroneously included in the group of laryngeal tumors and called "extrinsic" carcinomas of the larynx together with other tumors which actually arise within the larynx.

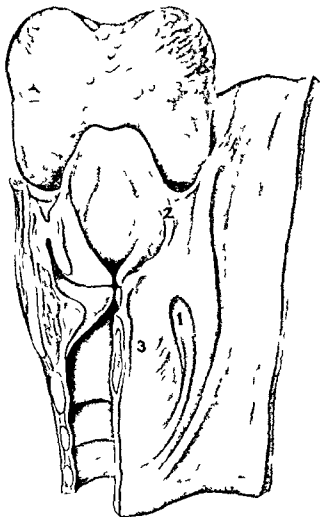


Fig. 275.—Posterior view of the larynx and laryngopharynx showing 1 piriform sinus, 2 arytenoepiglottic fold and 3 posterolateral region. On the left side a section of the larynx allows a view into this organ.

The usual points of origin of carcinoma of the laryngopharynx are (1) posterior wall (2) lateral wall of the piriform sinus (3) medial wall of the piriform sinus and (4) posterolateral region. In this group we are also including the rather common carcinoma of the arytenoepiglottic fold which arises from the limiting border of the hypopharynx and endolarynx and anatomically belongs as much in one as in the other of these regions. Not included in this group



pharynx and the endolarynx. These limits are formed by the free borders of the epiglottis anteriorly and the arytenoepiglottic folds which continue them in a posterior and downward direction toward the arytenoids and finally the interarytenoid space in the posterior midline.

The lining of the hypopharynx is formed by stratified squamous epithelium beneath which are abundant mucous glands.

**Lymphatics**—The many lymphatics of the laryngopharynx converge toward an orifice in the thyrohyoid membrane which is equidistant from the hyoid bone and the thyroid cartilage. This orifice also gives passage to the superior laryngeal artery. Through it the lymphatics find their exit and immediately form several diverging trunks which terminate in the anterior and external nodes of the internal jugular chain (Rouvière).

### Incidence and Etiology

Carcinomas of the laryngopharynx and of the limiting borders of the larynx are more common than carcinomas of the endolarynx proper. There are probably three or four hypopharyngeal tumors for every carcinoma of the endolarynx. These tumors are predominantly found in males between 40 and 60 years of age. One exception is notable—that of carcinomas of the posteriooid region the great majority of which are found in women. In a series of ninety-eight carcinomas of the posteriooid region reviewed by Turner, eighty-five were found in women.

Ahlbom has pointed out the frequency with which carcinoma of the oral cavity, pharynx, or esophagus in women is accompanied by a Plummer-Vinson syndrome (sideropenia). This syndrome has rarely been observed in the United States although it was described here. It is characterized by anemia, achlorhydria and general signs of atrophy of the mucous membrane, mouth, and pharynx. The disease is probably due to some alimentary deficiency. There is usually a history of loss of teeth in early life and chronic dysphagia. About 25 per cent of the patients show moderate enlargement of the spleen, and koilonychia (spoon-shaped nails) is also often observed. This syndrome is a true precancerous condition which may be present for many years before any manifestation of cancer is found. At the Radiumhemmet in Stockholm, where carcinomas of the hypopharynx have been more frequently found in women than in men, Ahlbom observed that most cases were associated with a Plummer-Vinson syndrome.

### Pathology

**Gross Pathology**—Carcinomas of the *posterior wall* of the hypopharynx usually extend diffusely and present a central fissurelike ulceration which rapidly becomes necrotic (Fig 278). They habitually infiltrate downward toward the esophagus but seldom invade the prevertebral muscles or any important structure. Then adenopathy is usually bilateral.

Carcinomas of the *lateral wall of the piriform sinus* rapidly invade the lateral wing of the thyroid cartilage. Partly because of the trauma of deglutition and also because of the infiltrating nature of these tumors, an extensive

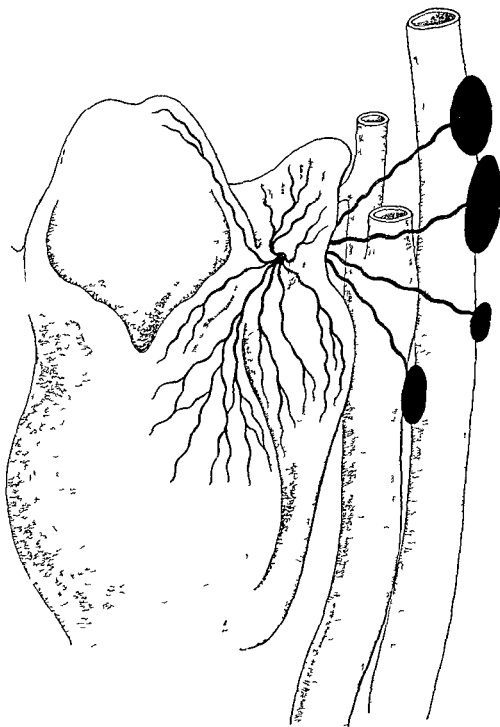


Fig 2<sup>nd</sup>—Lymphatics of the laryngopharynx

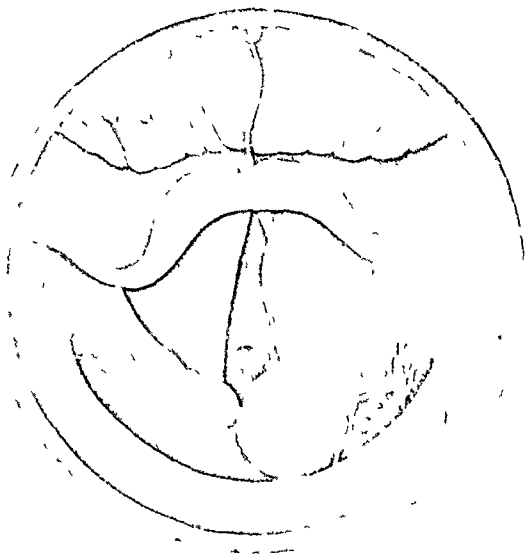


FIG. 280.—Mirror view of a carcinoma of the medial wall of the piriform sinus showing considerable edema of the arytenoid and aryepiglottic fold and a tumefaction of the left false cord hiding the true cord. Because of the marked edema these tumors are easily confused with primary carcinomas of the endolarynx and are usually classified as such. Actually the primary lesion is outside of the anatomic limits of the endolarynx.

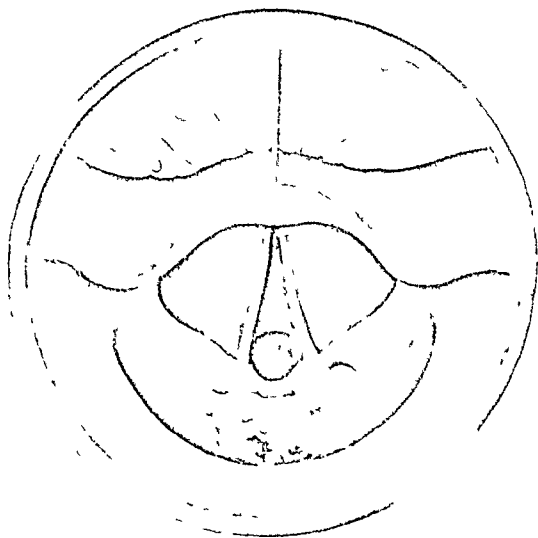


FIG. 281.—Mirror view of a carcinoma of the posterioval region. These tumors occur predominantly in women although carcinomas of the laryngopharynx in women are not common.

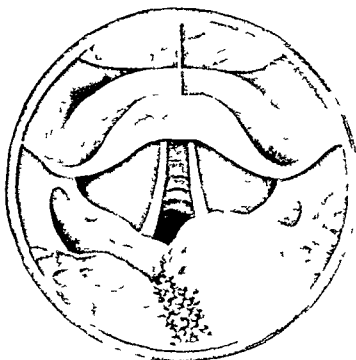


Fig 278—Laryngeal view of a carcinoma of the posterior wall of the laryngopharynx showing fissurelike ulceration surrounded by nodules

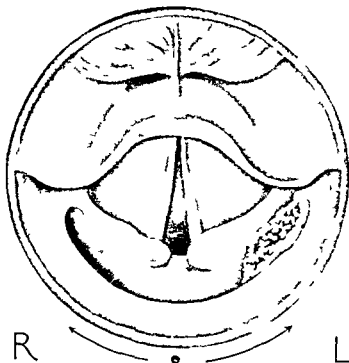


Fig 279—Carcinoma of the lateral wall of the piriform sinus without invasion of the larynx and showing only a slight edema of the arytenoid

area of necrosis develops (Fig 279) This sometimes dissects on both sides of the thyroid wing and may produce an external tumefaction on the side of the larynx Tumors of the lateral wall of the hypopharynx may rapidly invade the internal carotid A unilateral adenopathy is almost always present

Carcinomas of the *medial wall of the piriform sinus* may rapidly invade the larynx through the laryngeal ventricle, the true cord may be infiltrated, and the false cord becomes edematous (Fig 280) Invasion of the outer aspect of the cricoid cartilage may occur, but this is not frequent A unilateral mid-cervical adenopathy may or may not be present

Carcinomas of the *postcricoid region* are usually well-differentiated nodular tumors arising on the mucous membrane of the mouth of the esophagus anteriorly (Fig 281) They infiltrate insidiously the anterior wall of the esophagus where they seem to develop rather rapidly The growth may become annular once it descends into the esophagus proper As a consequence of the development, the larynx and the trachea are displaced forward A lower cervical adenopathy is present only in a few cases

Cancer of the *arytenoepiglottic fold* is usually an exophytic, typically "cauliflower" type of growth (Fig 282) The tumor is friable and extends over both the laryngeal and pharyngeal aspects of the arytenoepiglottic fold (Fig 283) As a consequence there is obstruction of the piriform sinus and neighboring edema of the false cord A midcervical or lower cervical adenopathy is practically always present

Due to the considerable secondary infection which usually accompanies these tumors, and also because they hinder deglutition, *necrotizing bronchopneumonia* (aspiration pneumonia) may develop Necrosis of the bronchial walls and suppuration of the lung parenchyma are invariably present The distribution is lobular and localized to one or more bronchopulmonary segments The bronchi are diffusely infected and may contain purulent material Central softening of the involved areas and often occasional small abscesses may be found (Ackerman)

**METASTATIC SPREAD**—The majority of carcinomas of the hypopharynx when first seen present metastatic cervical adenopathy situated along the course of the internal jugular chain of nodes In general the metastatic nodes are voluminous, not very hard, and usually surrounded by peradenitis In a few rare instances the adenopathy may consist of a group of small hard nodes which accompany the more differentiated type of tumor As a general rule the metastatic nodes will be found in the midcervical region, but some carcinomas of the piriform sinus and arytenoepiglottic fold may give a low cervical metastasis which develops toward the supraclavicular fossa

Cancer of the laryngopharynx tends to spread toward the mediastinum through lymphatic permeation In addition, rapid invasion of the internal jugular vein by the metastatic growth may produce cancerous thrombosis which easily induces blood-borne pulmonary metastases In sixty-two autopsies of cases with metastatic carcinoma of the neck, Willis found twenty-nine cases of invasion of the jugular vein, twenty-four of which had visceral metastases

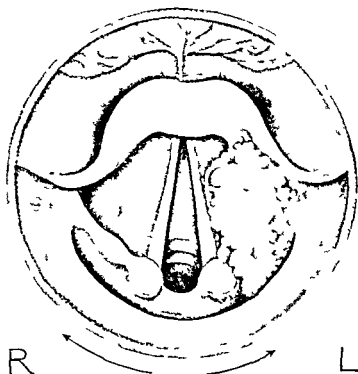


Fig 282.—Mirror view of a carcinoma of the arytenoepiglottic fold showing a typical exophytic growth extending over the laryngeal wall of the epiglottis and over the false cord with some diminution of the movements of the larynx due to mechanical obstruction

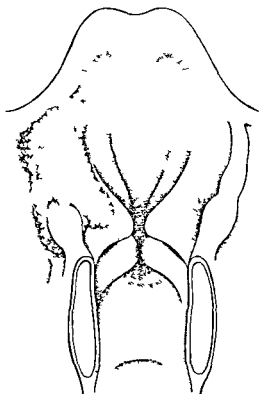


Fig 283.—Posterior view of a carcinoma of the arytenoepiglottic fold of the preceding figure showing superficial extension to the epiglottis arytenoid piriform sinus and false cord

of the pharynx are not often seen, but this is because so few are locally sterilized that the patient does not live long enough for the development of such metastases.

It has been mentioned before that because of dysphagia and accompanying malnutrition and because of frequent secondary infection and necrosis, a particular type of aspiration pneumonia may develop. This may occur before, during, or after treatment. It is usually accompanied by only slight fever but a rapid pulse. Because of these factors (loss of weight, absence of fever, poor general condition), the patient may appear to be the subject of a generalized metastatic spread.

### Diagnosis

The diagnosis of tumors of the laryngopharynx by indirect pharyngoscopy offers little difficulty. Even in those cases where the cooperation of the patient cannot be immediately secured, repeated examinations through the mirror will contribute more information than will be obtained by direct pharyngoscopy.



FIG. 284.—Sketch of a roentgenogram of the pharynx and larynx in a case of carcinoma of the lateral wall of the piriform sinus showing invasion of the thyroid cartilage with fracture of its superior horn.

**Roentgenologic Examination**—The examination is not complete without a profile roentgenogram of the soft tissues of the neck, for it will contribute further details as to the topography of the tumor and invasion or displacement of the laryngeal cartilages (Fig. 284). This information is of value in out-

**Microscopic Pathology**—The overwhelming majority of tumors of the hypopharynx are epidermoid carcinomas most of which are rather undifferentiated. In general, however, they are less differentiated than carcinomas of the endolarynx.

### Clinical Evolution

The most common first symptom of carcinomas of the hypopharynx is the appearance of *odynophagia*, which is sometimes unilateral. Progressive *dysphagia* will also be present and this will rapidly contribute to loss of weight and *asthenia*. *Otalgia* on the same side as the lesion often follows closely the appearance of the first symptom. *Hoarseness* is only present when the tumor has invaded the larynx or produced sufficient displacement of it to interfere with phonation. *Cough*, particularly after ingestion of food, may be present, and in some cases it is almost constant. *Dyspnea* is very rare being present more often in those tumors of the piriform sinus which invade the larynx and obstruct the glottis. In general, respiratory difficulty, when present is not very marked. Local pain in either side of the neck may occur and will be particularly intense in those tumors which have invaded the cartilaginous structures of the larynx. *Hemoptysis* is very rarely observed, but when present, is serious, betraying in most instances the invasion of the carotid.

Most tumors of the hypopharynx are secondarily infected and necrotic causing *malodorous breath*. Occasionally there may be *expectoration* of necrotic material, fragments of the tumor, or cartilage.

Metastatic nodes in the cervical region are most often unilateral. They follow closely the appearance of the first symptoms, but in some instances the *adenopathy may be the first clinical sign of disease*. This may lead to an erroneous diagnosis if the primary lesion is not suspected. These metastatic nodes usually grow rapidly and become voluminous. They are soft and movable and may be found anywhere along the sternocleidomastoid muscle but most commonly are present in the midcervical region. However, submaxillary and supraclavicular nodes may also be observed. This type of adenopathy seldom produces pain but when pain is present it is associated with small nonconfluent hard, rapidly fixed nodes (well differentiated carcinomas).

Some tumors of the lateral wall of the pharynx present a tumefaction in the midcervical region at the level of the posterior border of the thyroid cartilage. This tumefaction is usually due to direct extension of the tumor and secondary infection and should not be confused with an adenopathy. Carcinomas of the mouth of the esophagus may displace the larynx and trachea forward and give a clinical impression of goiter.

Distant metastases are seldom found in the early stages of the disease but they usually develop sometime during its course. Coutard reported on eighty-nine patients with carcinoma of the hypopharynx, nineteen of whom (21 per cent) remained locally cured two years after roentgentherapy. Ten of these nineteen patients died from pulmonary, hepatic and osseous metastases three to seven years after the treatment while the primary lesion was apparently controlled. It is obvious that distant metastases from carcinoma



they are present mostly in the lower lobes (Fig 287) These changes are characterized by a patchy cloudiness, but, as the disease progresses, areas of rarefaction may appear in the center of the opaque areas (LeMone)

The retropharyngeal abscess is a soft, fluctuant, nonulcerated hemispheric tumefaction arising from the lateral and posterior wall of the hypopharynx. This benign condition offers the most common problem of differential diagnosis. Digital palpation will probably be sufficient to establish the diagnosis.



Fig. 286—Sketch of a roentgenogram in a case of carcinoma of the posterocold area showing obstruction of the trachea by a tumor developing on the anterior wall of the esophagus. A small amount of barium helps in demonstrating that most of the tumor is on the anterior wall of the esophagus.

### Treatment

**SURGERY**—Although a good approach to these tumors may be had by a lateral or medial pharyngotomy, complete excision of laryngopharyngeal tumors is practically impossible. Moreover, the operation is contraindicated because of the usual undifferentiated pathologic character of these tumors and the invariably accompanying metastases. New reported on three patients with tumors of the hypopharynx treated surgically, one of whom survived seven years but died of local recurrence.

Since irradiation is of no avail in the treatment of the posterocold carcinomas and because adenopathy is rare in such cases, surgical eradication is justified. This usually implies the necessity of a laryngectomy and laborious plastic repair of the pharynx. Under very skilled hands, this procedure has

lining the position and size of the fields of irradiation. In tumors of the retrocricoid area and in some tumors of the piriform sinus, the simple profile roentgenogram may be complemented by another taken while maintaining air under pressure in the pharynx (Valsalva's maneuver). This procedure allows a certain amount of air to enter the upper portion of the esophagus and gives a better outline of the region which is being investigated. Also in tumors of this region, added information may be obtained by taking roentgenograms immediately after the patient swallows a spoonful of thick opaque material (Fig. 286).

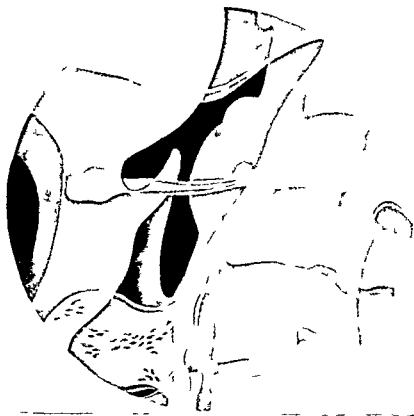


Fig. 286.—Sketch of a roentgenogram in a case of carcinoma of the posterior wall of the laryngopharynx. Notice marked thickening of the posterior wall and irregularities in its outline.

**Biopsy**—A biopsy can always be easily obtained from tumors of the hypopharynx through direct or indirect pharyngoscopy. The only difficulty is that very often only necrotic material is obtained at the first trial and the biopsy has to be repeated. An aspiration biopsy of metastatic cervical nodes should always be performed as a matter of record.

**Differential Diagnosis**—A roentgenogram of the chest should always be taken in patients with carcinoma of the hypopharynx for investigation of mediastinal metastases. But in cases of accompanying bronchopneumonia, it should not be forgotten that a roentgenogram of the chest may give the false impression of pulmonary metastases. It should be noted however, that the changes found in aspiration pneumonia have a lobular distribution and that

One of the reasons for the necessity of protracted treatments is the large size of field usually necessary for the irradiation of these tumors, for, in general, it is more satisfactory to treat both the primary lesion and the metastases in the same field. In rare instances it may be preferable to treat them separately. The large size of field implies greater general reactions on the part of the patient and also more marked reactions of the skin, mucous membrane, and vasculoconnective tissue. These reactions cannot be avoided but they may be brought to a minimum by the use of small daily doses and careful clinical observation. As the tumor and its adenopathy reduce in volume, the size of the field may be diminished proportionately and the daily dose increased. At any rate, carcinomas of the laryngopharynx, unlike some laryngeal carcinomas, do not seem to require a high daily dosage.

Irradiation through excessively large fields, including the entire potential area of metastasis from the mastoid to the clavicle, leads only to failure. In practice, the field of irradiation should include the entire tumor area but should be as small as possible.

In studying his large series of treated carcinomas of the upper air passages, Coutard noticed that the greatest number of cured patients had been given treatment in fourteen, twenty-eight, and forty-two days. These periods of time correspond to the usual appearance of radioepithelitis of the mucous membrane (fourteen days) and radioepidermitis of the skin (twenty-eight days) and led to the hypothesis that there was a certain periodicity in the radio-sensitivity of epidermoid carcinomas. On this basis, Coutard conducted his treatments in periods of six weeks, giving a maximum daily dose around the end of the second, the fourth, and the sixth weeks. This has not as yet contributed any improved results, but the technique is an interesting one with applicable advantage in certain cases, as, for instance, in the treatment of solitary adenopathies.

Because radical neck dissections after radiotherapeutic treatment of primary lesions of the tongue have been so successful, it has been suggested that cervical adenopathies from carcinomas of the hypopharynx also be treated surgically after roentgentherapy to the primary lesion. Others deny the value of neck dissection in these instances and advise the implantation of radium emanation seeds into the metastatic node after surgical exposure. These combined procedures do not take into consideration that most failures in the treatment are due either to nonsterilization of the primary lesion rather than that of its metastatic implant or to the failure to heal a large area of deep seated pharyngeal necrosis. A thoroughly planned course of roentgentherapy to the primary and secondary lesions is most satisfactory, although not always successful.

Daily observation of the tumor during the course of roentgentherapy will contribute the best information as to its radiosensitivity by observing the rate of its regression as well as that of its adenopathy. This is of utmost importance, for by close scrutiny the reactions of the mucous membrane and of the skin may be kept within safe bounds. Proper nourishment of the patient, by

given some fair results. Graham reported that of a group of fifteen patients with carcinomas of the posterior area who had radical operations, two were living for periods of fifteen and twenty four years, respectively.

When dysphagia has become very marked, nourishment has to be administered through a nasal catheter. This method will often eliminate the aspiration of fluid into the bronchi. However, in extreme cases the passage of a catheter is not always possible and a gastrotomy may be necessary. In those patients in whom invasion of the larynx has resulted in a glottic or supra-glottic obstruction, the respiratory difficulty may be such that a tracheotomy is indicated. However, in the majority of cases, the respiratory difficulty will be due to supraglottic obstruction for which a tracheotomy is unnecessary.



Fig. 237—Roentgenogram of the chest showing typical necrotizing pneumonia characterized by patchy areas of increased density which could be confused with metastatic carcinoma. (From Ackerman L. V., Wiley H. and Le Mone D. V. *Am. J. Roentgenol.* 1945.)

**ROENTGENTHERAPY**—Early trials of roentgentherapy consisting of large total doses over a short period of time for carcinomas of the laryngopharynx offered nothing but a certain amount of palliation. Contard, in elongating the treatment over a period of several weeks, conducted his treatment under clinical control and for the first time roentgentherapy contributed permanent cures. Protraction of roentgentherapy over a period of five to six weeks allows the administration of a sufficiently large total dose while it eliminates the disadvantage of general reaction of the patient and diminishes the risk of radionecrosis frequently resulting from an excessive daily dosage.

The relative prognosis is best established on the basis of point of origin. Most curable among these carcinomas are those arising on the posterior wall of the pharynx which seldom invade any vital organ. Carcinomas of the arytenoepiglottic fold, even though voluminous and accompanied by large metastatic nodes, also have a favorable prognosis (Regato). Carcinomas of the piriform sinus, whether of the medial or lateral walls, are seldom curable.

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### CARCINOMA OF THE ENDOLARYNX

There is at present unquestionable confusion in the medical literature as to the definition of a carcinoma of the larynx. Many carcinomas actually arising and developing inside the larynx are called "extralaryngeal," and usually carcinomas which arise outside of the larynx itself are also called laryngeal tumors.

Originally the terms *intrinsic* and *extrinsic* were meant to define tumors arising respectively inside or outside of the larynx but which in one way or another affected the laryngeal structures. Because the term *intrinsic* was made synonymous with operable carcinoma of the larynx, its significance has varied with the concept of operability, and consequently it has not had the same meaning through the time, nor does it mean the same thing to the different authors. Most surgeons use the term *intrinsic* to define carcinomas of the glottis, that is, actually of the vocal cord or anterior commissure. It would be more logical to call those tumors carcinomas of the vocal cord than to give them the confusing term of intrinsic carcinomas.

The most common cause of failure to cure these tumors is the extensive destruction of tissue by the tumor and lack of proper repair. This is particularly true when the patient is in poor general condition. Sometimes the carcinoma is less radiosensitive because of secondary infection and coexisting edema, and its sterilization is consequently impossible. Finally, some patients die during the course of treatment or shortly afterward from pulmonary complications. A fatal hemorrhage sometimes occurs suddenly in the course of treatment of carcinoma of the lateral wall of the pharynx.

If bronchopneumonia should occur, its best treatment is roentgentherapy given through large fields to both lung areas. Ackerman reported on a series of fourteen patients with necrotizing pneumonia, two of whom recovered after radiotherapy of the lung areas. He pointed out the lack of effectiveness of sulfonamides in these patients. Streptomycin may prove to be an effective agent

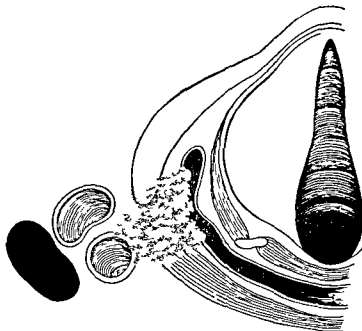


Fig. 238—Schematic representation of a carcinoma of the lateral wall of the piriform sinus infiltrating the thyroid cartilage and the common carotid artery. In these cases fatal hemorrhage in the course of treatment is not uncommon.

### Prognosis

In the treatment of carcinomas of the laryngopharynx, permanent cures are only obtained through painstaking administration of roentgentherapy. Coutard reported on a series of 200 patients with carcinoma of the hypopharynx of whom twenty three (11 per cent) were well and without symptoms five years or longer. Coutard observed that although 60 per cent of these patients were well one year after the treatment, this figure rapidly dropped to 30 per cent at the end of the second year because of local recurrences. The number of cures dropped in the succeeding years mostly because of distant metastasis.

It may be concluded that patients with carcinoma of the hypopharynx treated by roentgentherapy who have lived two years after treatment, have greater chances of developing a distant metastasis than a local recurrence.

membrane (Fig 290) Immediately below, the false cords are found the laryngeal ventricles or ventricles of Morgagni Their roof is formed by the false cords and their floor by the upper surface of the true cords Laterally the ventricles lie very close to the wing of the thyroid cartilage and posterolaterally they are very near the anterior limits of the piriform sinus, separated only by a thin layer of muscle, connective tissue, and mucous membrane (Fig 276)

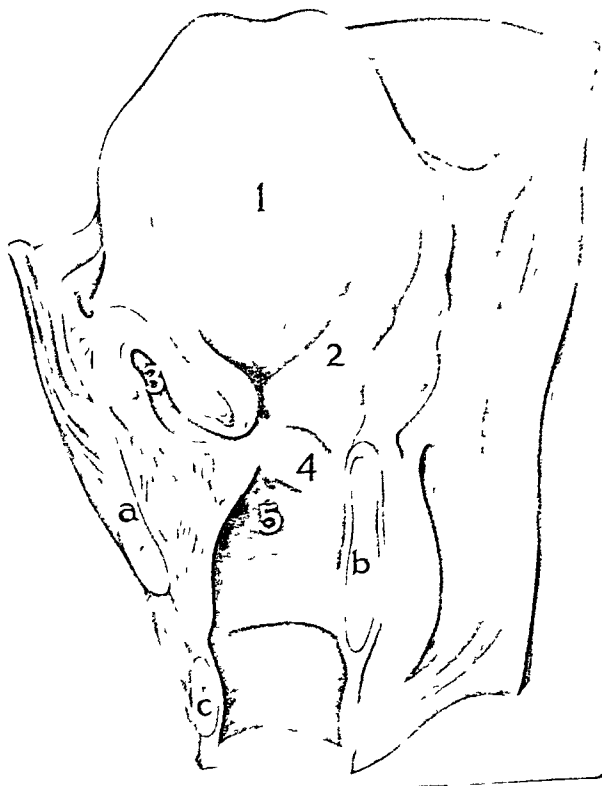


Fig 289—Posterior view of the larynx with a frontal section through the left half. 1 Laryngeal wall of the epiglottis 2 false cord 3 ventricle of Morgagni 4 vocal cord and 5 subglottic area Notice also a section of the thyroid cartilage b and c sections of the cricoid cartilage at different levels

The glottis is formed by the true vocal cords, which extend from the anterior angle of the thyroid cartilage to the arytenoids. Only their inner edge is visible on laryngeal examination. Laterally they continue horizontally to form the floor of the ventricle. Below the glottis the larynx has the shape of an inverted funnel. The subglottic region is just immediately below the true cords. At this level the lumen of the larynx is considerably smaller than

It is reasonable to include in the same group all carcinomas of the endolarynx, whether they are operable or not, mainly because of the fact that unlike laryngopharyngeal tumors they rarely metastasize to the cervical nodes. Also, endolaryngeal carcinomas have a more favorable prognosis in general than tumors of the hypopharynx.

The term carcinoma of the endolarynx includes all those tumors arising from the various laryngeal structures. The differentiation of the point of origin of these tumors is important in determining the treatment and for establishing the prognosis. Indeed, in some extensive cases, it may be impossible to establish this point of departure, but this is no argument against the classification of earlier cases whenever possible. The point of origin may make itself evident in the course of radiotherapy. These points of origin of carcinoma within the larynx present different clinical, pathologic, and diagnostic features which will be described separately. The following points of origin are recognized as separate clinical entities: carcinoma of the laryngeal wall of the epiglottis, carcinoma of the false cord, carcinoma of the laryngeal ventricle, carcinoma of the true cord, carcinoma of the subglottis.

Excluded from this group are tumors arising in the arytenoepiglottic fold or free border of the epiglottis, which actually develop on both sides of the limiting lines of the endolarynx. These tumors have a different pathologic character and are considered separately in the chapters on laryngopharyngeal and oropharyngeal tumors.

### Anatomy

The larynx is situated in front of and just immediately below the hypopharynx. The skeleton of the larynx is formed by three main cartilages: the epiglottis, the thyroid, and the cricoid, which are strongly interconnected by ligaments. In addition, just on the rim of the cricoid posteriorly and on both sides of the midline there are the arytenoid cartilages and the cartilages of Santorini, which are covered by numerous muscles and lined by a columnar ciliated epithelium. It is only on the free border of the true cord and on isolated areas of the false cords that the mucosa of the larynx is squamous in nature. The number of areas of squamous metaplasia increases with age.

The endolarynx is usually divided into three portions: the vestibule or supraglottic portion, the glottis, and the subglottic portion. The vestibule is formed anteriorly by the laryngeal wall of the epiglottis. This is a triangular surface extending from the free border of the epiglottis to the anterior commissure of the vocal cords (Fig. 289). Laterally the vestibule is formed by the false cords, which are made up of elastic tissue covered by mucous membrane and which extend from the laryngeal wall of the epiglottis to the arytenoids. Posterolaterally the false cords are continuous with the arytenoepiglottic fold which forms the posterolateral rim of the larynx. Just behind the false cords and on each side of the midline are found the arytenoids. These are two globular structures separated by a small space and composed of the arytenoid cartilages, ligaments, connective tissue and the overlying mucous



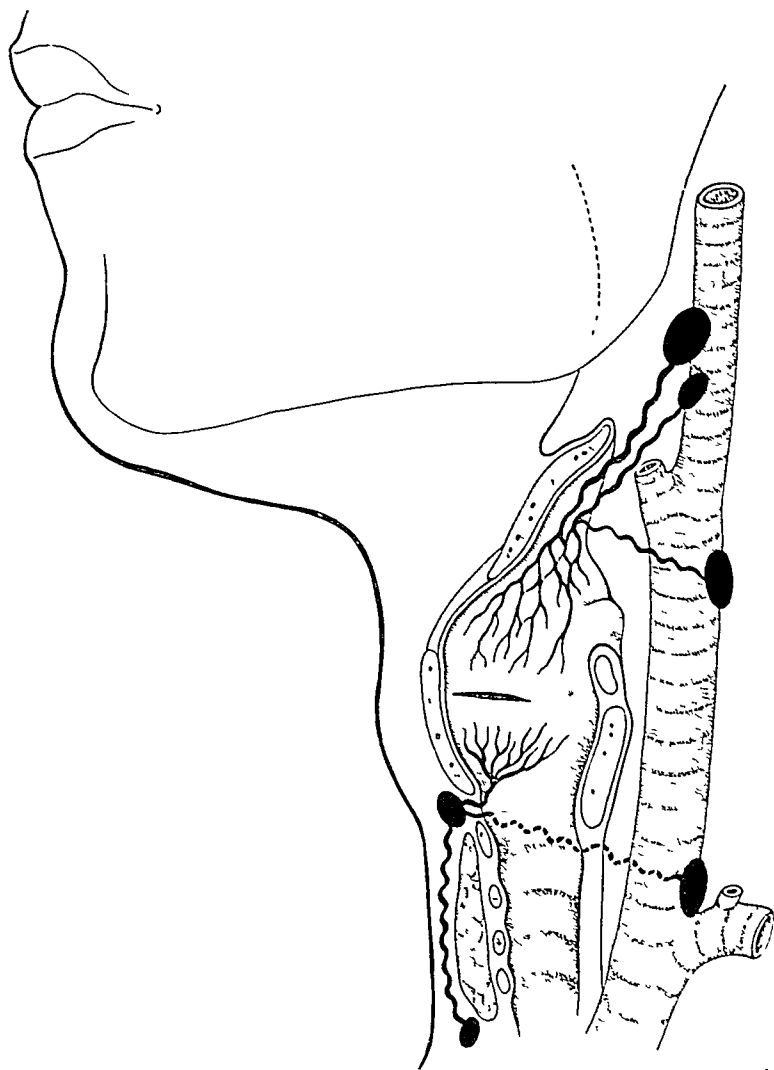


FIG. 291.—Lymphatics of the endolarynx. Notice the scarcity of lymphatics at the level of the glottis. The lymphatics of the supraglottic area are richer, ending in the nodes of the anterior jugular chain. The lymphatics of the subglottic area may end in a pretracheal node in the midline and rarely in a lower cervical node.

in the supraglottic region and it lacks the ability to expand because of the heavy cricoid cartilage which surrounds it

**Lymphatics**—The network of lymphatics of the endolarynx is rather sparse, particularly at the level of the glottis. The lymphatics of the supraglottic region are richer, particularly on the superior surface of the false cords. Some of these lymphatics, after perforating the thyrohyoid membrane, end in the

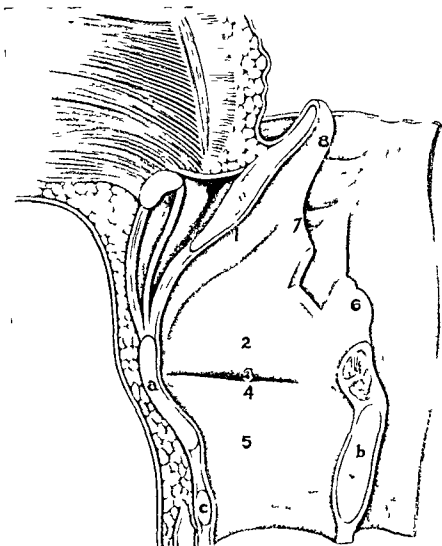


Fig. 290—Lateral view of the larynx showing a a cross section at the anterior midline of the thyrohyoid cartilage b and c sections of the cricoid cartilage 1 the laryngeal wall of the epiglottis and its close relation with the pre-epiglottic space 2 false cord 3 opening of the laryngeal ventricle 4 true cord 5 subglottic area 6 arytenoid region 7 arytenoepiglottic fold with a rectangular section to show its thickness and relationship to the piriform sinus and 8 free portion of the epiglottis

jugular nodes of the upper cervical region (Fig. 291). The few lymphatics of the subglottic region end in a pretracheal node in the lower anterior midline of the neck.

The lymphatics of the endolarynx are meager by contrast with those of the pharyngolarynx.

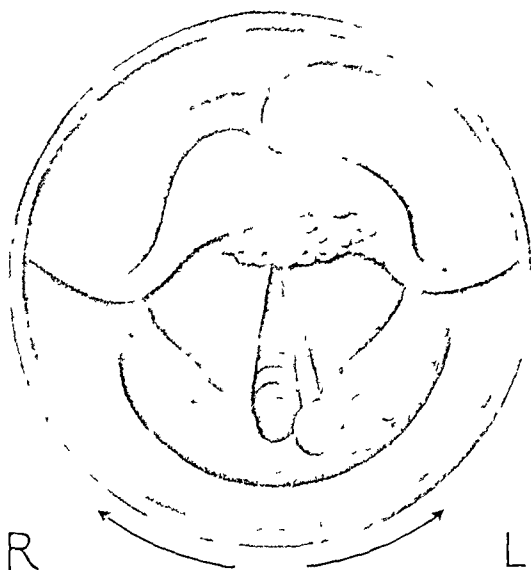


Fig. 292—Mirror view of a tumor of the laryngeal surface of the epiglottis showing some distortion and tumefaction in the left vallecula

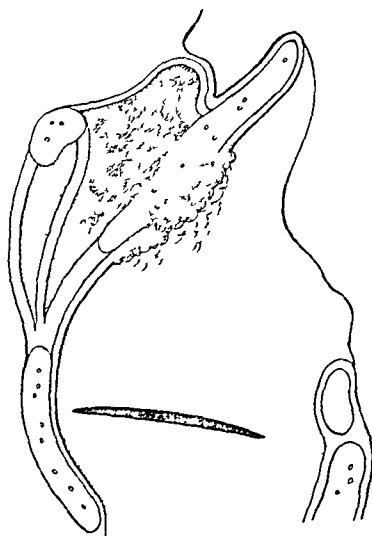


Fig. 293—Schematic representation of a tumor of the laryngeal wall of the epiglottis with extension to the pre-epiglottic area through the epiglottic cartilage

### Incidence and Etiology

Carcinoma of the endolarynx constitutes about 1 per cent of all forms of cancer. It is infrequently found in Negroes and the yellow races. It is most often found in men in their fourth, fifth, and sixth decades. It is very rare in women (approximately 2 per cent). Syphilis and tobacco have been incriminated as causative agents, but syphilis apparently plays a more important role in carcinoma of the tongue, and the new generation of female smokers has not produced any appreciable increase in the proportion of carcinomas of the larynx in women. Carcinoma of the larynx does not seem to occur more frequently in patients with chronic cough or expectoration both of which expose the larynx unquestionably to a great deal of chronic irritation. Vocal excess may be a factor in some cases.

### Pathology

**Gross Pathology**—Tumors of the endolarynx most frequently present a combination of ulceration and outgrowth. They infiltrate in different directions and invade different structures, depending on their point of origin.

Carcinomas of the *laryngeal surface of the epiglottis* arise almost in direct contact with the epiglottic cartilage. They easily invade and perforate this structure and extend without resistance into the pre epiglottic space (Fig 293).

Carcinomas of the *false cord* usually arise on the anterior half of its surface, close to the laryngeal wall of the epiglottis (Figs 294 and 295). The base of the ulceration may be necrotic and there will usually be some surrounding edema which may include the arytenoid. In their lateral extension, they often reach the thyroid cartilage and may invade it (Fig 296). They also may extend anteriorly toward the laryngeal wall of the epiglottis and to the false cord of the opposite side. In this process the laryngeal ventricle becomes obliterated (Fig 296), and the tumor may come in contact with the true cord but actual invasion of the true cord only occurs in advanced cases.

Carcinomas of the *laryngeal ventricle* are probably more common than has been suspected. The ulceration is usually hidden within the ventricle. The tumor extends toward the false cord, producing a bulky, nonulcerated tumefaction on the laryngeal vestibule (Fig 298). Invasion of the thyroid cartilage occurs almost constantly and early in the development of these tumors (Fig 299). The thin layer of muscles lying next to the lateral wing of the thyroid is also invaded and the skin ulcerated in late stages. Posterolateral extension of tumors of the laryngeal ventricle results in obliteration of the piriform sinus but seldom in ulceration of the mucous membrane in this area.

*True cord* is the most common of all the single points of origin of carcinoma within the larynx. Early lesions appear as nonulcerated tumefactions of the anterior third of the true cord or as papillary growths with a typical ragged appearance (Figs 300 and 301). As the disease extends there may be accompanying edema of the false cord. There is often extension to the opposite vocal cord through the anterior commissure. Infiltration of the subglottis is not uncommon (Fig 304). Carcinomas of the vocal cord may easily invade the thyroid cartilage at the lower half of its anterior midline.

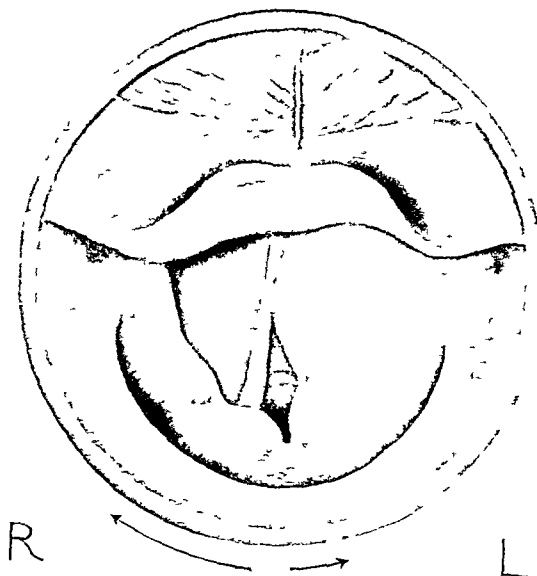


Fig. 297—Mirror view of a carcinoma of the laryngeal ventricle showing deformity of the false cord the arytenoid and arytenoepiglottic fold with obliteration of the piriform sinus and diminution of the mobility of the left hemilarynx. No ulceration is seen.

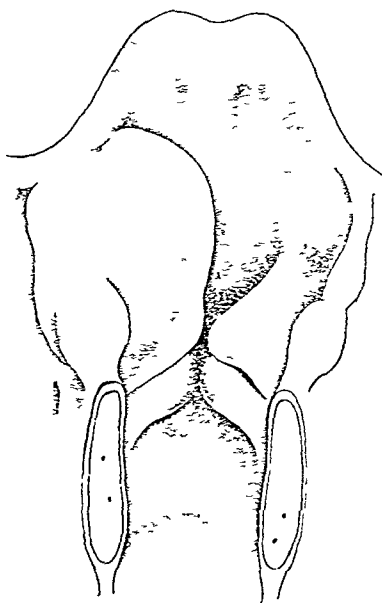


Fig. 298

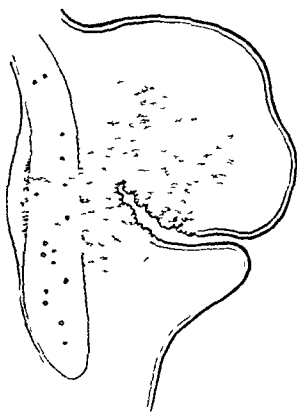


Fig. 299

Fig. 298—Posterior view of a carcinoma of the laryngeal ventricle. The ulceration is hidden within the ventricle and nothing but considerable deformity can be observed.

Fig. 299—Schematic frontal section of carcinoma of the laryngeal ventricle showing marked deformity infiltration of the thyroid cartilage and outside tumefaction.

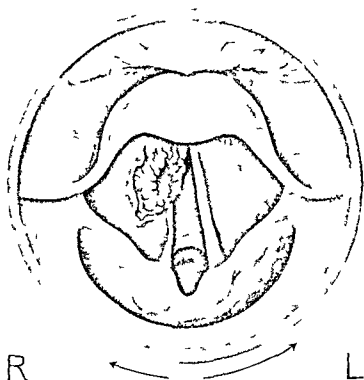


Fig 294—Mirror view of a carcinoma of the right false cord partially hiding the true cord with a slight edema of the arytenoid and diminution of mobility of the right hemilarynx

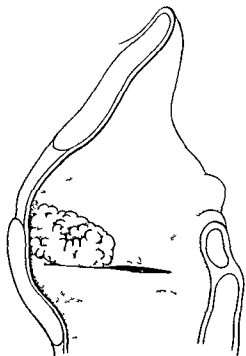


Fig 295

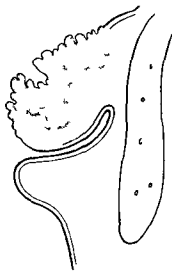


Fig 296

Fig 295—Lateral view of the carcinoma of the false cord shown in Fig 294

Fig 296—Frontal section of a carcinoma of the false cord illustrating the obliteration of the ventricle and infiltration close to the thyroid cartilage

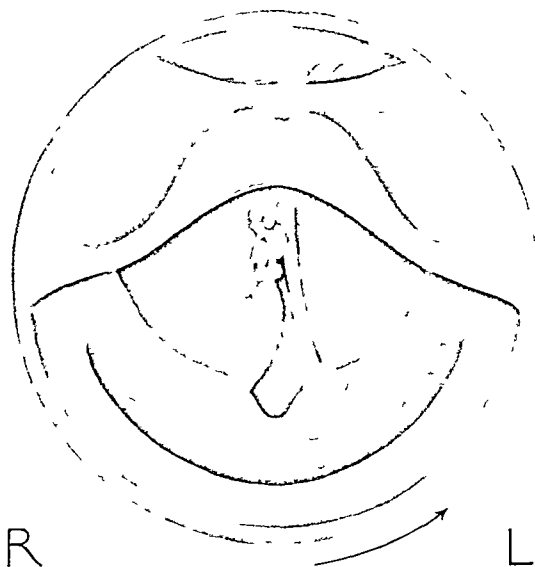


Fig 303—Mirror view of a carcinoma of the true cord showing some papillary outgrowth on the anterior half but also edema of the posterior half with fixation of the right hemilarynx. The presence of edema and fixation denotes infiltration beyond the visible areas.

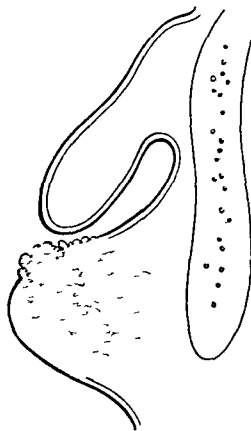


Fig 304—Frontal section of an infiltrating carcinoma of the true cord showing some subpottic edema and diffuse infiltration of the surrounding tissues.

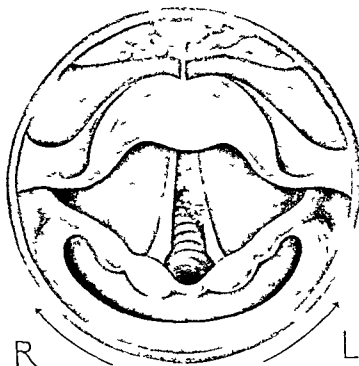


Fig. 300.—Mirror view of an early carcinoma of the anterior half of the true cord showing papillary outgrowth and perfect mobility of both sides of the larynx

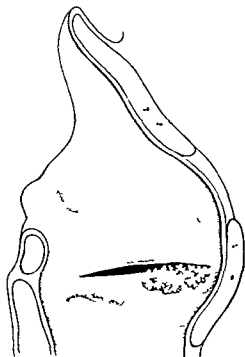


Fig. 301

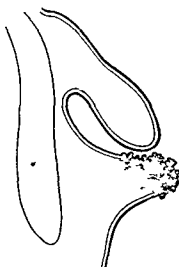


Fig. 302

Fig. 301.—Lateral view of a papillary carcinoma of the true cord

Fig. 302.—Frontal section of an early carcinoma of the buccal cord showing mostly papillary outgrowth and practically no infiltration



Carcinomas of the *subglottis* are usually submucous tumefactions adherent to the cricoid cartilage and with little superficial ulceration (Fig 306). Deep infiltration of the cord is usually present, but rarely this will result in an ulceration. Subglottic lesions usually develop on the anterior half of this narrow space.

**METASTATIC SPREAD**—Metastases occur only very rarely in carcinomas of the endolarynx. Because of conflicting classifications, it is impossible to give a true incidence of metastases. When the above classification is adopted and all these tumors are included as carcinomas of the endolarynx, about 10 per cent of the patients will show a metastasis some time during the course of the disease. The main offenders are the supraglottic tumors. Their metastatic nodes are found high in the anterior cervical chain. Occasionally a subglottic tumor will metastasize to a pretracheal node.

**Microscopic Pathology**—Although the lining of the endolarynx is formed by columnar epithelium, the overwhelming majority of carcinomas arising in this area are epidermoid in nature, developing by metaplasia. The most highly differentiated of these carcinomas, however, are found to develop from the true cord, the free border of which is covered by a squamous epithelium. Rare cases of adenocarcinomas of the endolarynx have been reported and also a few rare sarcomas. Most of the undifferentiated carcinomas of the larynx arise in the supraglottic area.

### Clinical Evolution

The most common presenting symptom in carcinoma of the endolarynx is *hoarseness*. The character of this hoarseness is an important factor in the clinical history. Patients with carcinomas of the vocal cord will usually have a progressively increasing hoarseness which might end in almost complete aphonia. Patients with tumors of the supraglottic area will usually present an intermittent hoarseness with intervals of perfectly normal voice.

*Dyspnea* is often found in patients with carcinoma of the endolarynx. It is practically never present or important in those with supraglottic tumors. With tumors of the vocal cord, the intensity of the dyspnea will usually depend on the presence or absence of subglottic extension. With tumors of the subglottis, dyspnea is often a presenting symptom and it rapidly becomes very marked.

*Cough* is not a common symptom. It may only occur after deglutition. Cough and associated expectoration may, however, be present in glottic and subglottic tumors. *Odynophagia* is more commonly associated with tumors of the laryngopharynx, but in advanced endolaryngeal cases it may also be present. *Otalgia* occurs on the same side as the lesion when there is abundant secondary infection. *Local pain* is exceptionally present and it is usually a sign of invasion of the cartilage. *Hemoptysis* is also uncommon but may be present in some vestibular tumors.

Left to themselves, carcinomas of the endolarynx will sooner or later occlude the air passage and necessitate a tracheotomy. Supraglottic tumors may extend to the free portion of the epiglottis and the arytenoepiglottic fold and be, in their later stages, unrecognizable from tumors which arise in these

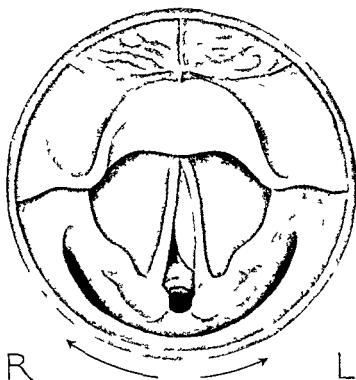


Fig. 303—Mirror view of a carcinoma of the subglottis showing no ulceration having displaced the left cord upward and diminished the mobility of the left hemilarynx. These cases are usually accompanied with marked dyspnea.

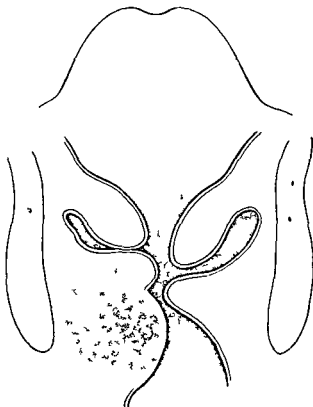


Fig. 304—Frontal section of a carcinoma arising in the subglottis. These are usually very infiltrating tumors showing submucous extension and very little ulceration.

the angle of the mandible. Less often a node may be found on the anterior lower midline of the neck in front of the trachea.

*Indirect Laryngoscopy*—When hoarseness is present, an indirect laryngoscopy should never be deferred. It is possible that the classic procedure for this examination, requiring a darkened room, a special floor lamp, and



Fig. 308.—Sketch of a roentgenogram of a normal adult male showing 1 hyoid bone, 2 thyroid cartilage, 3, cricoid cartilage, 4, base of the tongue, 5, vallecula, 6 free portion of epiglottis, 7, laryngeal wall of the epiglottis, 8, arytenoepiglottic fold and 9 laryngeal ventricle.

a head mirror, may account for the fact that few practitioners are ready to perform an indirect laryngoscopy. This examination requires no extraordinary skill and in these times, when all senior medical students know how to use an ophthalmoscope, it is indeed paradoxical that an indirect laryngoscopy

limiting areas. As it has been stated invasion of the skin in the anterior midline is not uncommon in advanced carcinomas of the ventricle. Death usually occurs because of pulmonary complications (Ackerman).

### Diagnosis

**Clinical Examination**—External inspection and palpation of the larynx is a very important factor which is usually disregarded. The larynx may be displaced and the symmetry of the thyroid cartilage disrupted when tumor after invading the cartilage, has spread over its external surface. The tumefaction so produced by direct extension should not be confused with metastatic adenopathy.



FIG. 307.—The lateral mobilization of the larynx produces a crackle which is absent when tumor of the larynx extends posteriorly.

The lateral mobilization of the larynx against the spine produces a noise the *thyrovertebral crackle*. This occurs on both sides of the midline by the contact of the posterior border of the thyroid cartilage and the cervical column. In carcinoma of the endolarynx this "crackle" may not be present on the side of the lesion which may be evidence that tumor has invaded posteriorly, interfering with the normal excursion of the thyroid cartilage. Neighboring edema may in itself suffice to give this impression, but the absence of the thyrovertebral "crackle" may be taken as a strong sign that tumor has extended beyond the limits for which a total laryngectomy would be successful.

Complete palpation of the neck will include the search for an adenopathy, a rare finding in carcinoma of the endolarynx. When a metastatic node is present it will be found more commonly on the anterior jugular chain below

**larynx** This is achieved alternately by requesting the patient to breathe deeply and to produce the sounds *eh* and *ee*. Only after repeated alternations of breathing and phonation can the anterior commissure of the vocal cords be seen. When a tumor is discovered, the exact limits of its extension and its effect upon the mobility of the larynx should be noted, as well as the symmetry or asymmetry of the piriform sinuses. When there is respiratory difficulty, it is important to note whether the obstruction is glottic, supra glottic, or subglottic.



Fig. 310—Sketch of a roentgenogram of the larynx in a case of carcinoma of the true cord showing early extension and destruction of the lower part of the cricoid cartilage on the anterior midline and extension to the subglottis.

On indirect laryngoscopic examination, it may sometimes be noted that the epiglottis is bent toward the posterior wall of the pharynx and that the vocal cords are not entirely visible. This usually occurs in tumors of the laryngeal wall of the epiglottis and is a warning against examinations that are not thorough. In tumors of the supraglottic area, the mobility of the larynx is seldom impaired unless it be by the bulk of the tumor itself. In tumors of the glottis and subglottis, the mobility of the larynx may be considerably diminished or entirely abolished on one side. This usually occurs because of infiltration of muscles.

The modern introduction of direct laryngoscopy with its undemable usefulness does not eliminate, and, in fact, cannot substitute entirely, an indirect laryngoscopy. The indirect laryngoscopy permits a stereoscopic view of the larynx with greater sense of depth and the movements of the larynx are

should be considered the gift of a specialist. Indirect laryngoscopic examination is greatly simplified by the use of a portable electric headlight.

For an indirect laryngoscopy, the patient should be sitting in front and slightly at a lower level than the examiner. In some instances a better view may be obtained with the examiner standing and with the patient's head hyperextended. This permits a good view of the anterior commissure of the

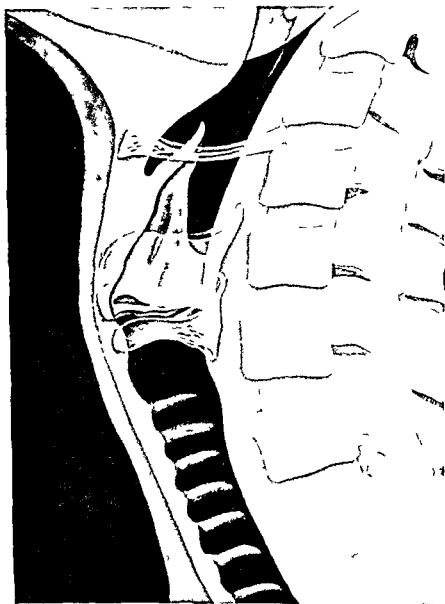


Fig. 10.—Sketch of a roentgenogram of the larynx of a normal adult female showing considerably less calcification of the cartilages and a smaller structure than in the male.

vocal cords. An anesthetic is not necessary as a general rule, and its use should be limited to those patients in whom complete relaxation is unobtainable. The patient must be entirely at rest (lax).

In an indirect laryngoscopy the examiner should observe the symmetry of the laryngeal structures and also of the movements of both sides of the

pret in view of the fact that the calcification of these cartilages is very variable. However, demineralization at the midline of the thyroid cartilage is practically a sure sign of invasion by tumor. This may be observed in either advanced tumors of the vocal cord or early carcinoma of the laryngeal ventricle (Fig. 312). A profile view of the soft tissue of the neck gives information as to the spread of the tumor in the sagittal plane but is not of much value in describing the transverse spread of these tumors.



FIG. 312 - Sketch of a roentgenogram in a case of carcinoma of the laryngeal ventricle showing extensive destruction of the thyroid cartilage on one side.

In 1936 Leboigne introduced the tomographic study of the normal and pathologic larynx. Tomography is also known as planigraphy, stitigraphy, laminography and body section radiography. Leboigne's exhaustive investigation of the normal and pathologic larynx is a definite addition to our means of examining this region of the body. The tomograms is a complement of the profile roentgenograms permit the almost exact evaluation of the spread of the tumor in all planes and are particularly useful in the tumors of the false cord (Caulk) and ventricle (Figs 313, 314 and 315).

**Biopsy**—In most instances of carcinoma of the endolarynx the diagnosis is clinically obvious. In every instance nevertheless microscopic proof is essential and accordingly a biopsy should be secured through indirect laryngoscopy. An effective local anesthesia is usually requisite. Biopsy of the larynx is often difficult requiring special instruments and considerable ex-

better appreciated. The direct laryngoscopy gives a monocular view of the larynx. Because of the trauma of the instrument used and the corresponding reaction of the patient, the larynx becomes rigid and quickly edematous. A direct laryngoscopy, however, is sometimes necessary for proper visualization of certain tumors of the laryngeal wall of the epiglottis or anterior commissure and for obtaining certain biopsy specimens.



FIG. 311.—Sketch of a roentgenogram of the larynx in a case of carcinoma of the laryngeal wall of the epiglottis showing irregularities in that area and decalcification of the thyroid cartilage on the anterior midline.

**Roentgenologic Examination**—Coutard introduced the radiographic examination of the larynx in 1922. This method of examination has become a valuable adjunct of the laryngoscopic examination in cancer of the endolarynx. A profile roentgenogram of the soft tissues of the neck is taken, centering the x-ray beam as accurately as possible at the level of the disease. This is a very important factor in the interpretation of the results, which requires a thorough knowledge of the radiographic appearance of a normal larynx as well as of the chronology of calcification of laryngeal cartilages in the normal individual. The radiographic examination gives a better perception of the topography of the tumor than the simple laryngoscopic examination. Some apparently small carcinomas of the vocal cord may show extensive invasion of the subglottis (Fig. 310).

Some carcinomas of the laryngeal wall of the epiglottis may have invaded the pre-epiglottic space (Fig. 311). By direct invasion, destruction of the laryngeal cartilages may have taken place but this is often difficult to inter-



and very rarely, if at all, primary in this organ. A radiographic examination of the lungs will consequently be of great value in establishing the differential diagnosis.

A *laryngocele* may be easily confused with a tumor of the laryngeal ventricle. They produce nonulcerated tumefactions of the false cord. However, they usually have a long history and intermittent periods of remission. Percussion of the area of the larynx will result in some cases in a peculiar unilateral resonance. A profile roentgenogram of the soft tissues of the neck may show an abnormal air bubble superimposed on the area of the false cord and epiglottis (Fig. 316). In these cases a tomogram of the larynx is very useful in revealing the existence of an air space lateral to the larynx (Fig. 315). The laryngocele may be filled with mucus and in that case it will be more difficult to diagnose.



Fig. 314.—Sketch of a tomogram of the larynx in a case of carcinoma of the false cord. Notice obliteration of the laryngeal ventricle and bulging into the piriform sinus. (From Dr. F. Leborgne, Director, Instituto de Radiología de la Asistencia Pública, Montevideo, Uruguay.)

*Keratosis* of the larynx (leucoplakia, pachyderma) is a relatively common benign condition most frequently observed in adult males, a certain number of these cases, however, either become or predispose to the development of carcinoma, although this cannot be anticipated in any case (Cleif). Patients with keratosis of the larynx should be observed closely.

Acute respiratory conditions may be the cause of hoarseness, but the differential diagnosis can be easily made when invasion of the mucosa is present and there is no tumefaction. Singer's nodes are small, salient points on the free surface of the true cords and are usually bilateral. Tuberculous tumefactions may be encountered, although rarely, in the interarytenoid space. *Papillomas* of the true cord are usually whitish, grapelike growths, usually pedunculated, and move easily in and out of the glottis with the movements

perience It should preferably be left to the specialist At times, the obtention of a biopsy is impossible as, for instance, in carcinomas of the laryngeal ventricle where the ulceration is not visible, and consequently the biopsy on the smooth surface of the tumefaction will bring nothing but normal epithelium Some advanced cases of carcinoma of the vocal cord which infiltrate upward may be accompanied by so much edema of the false cord that the ulceration is not visible In this case, however, the biopsy is possible through direct laryngoscopy

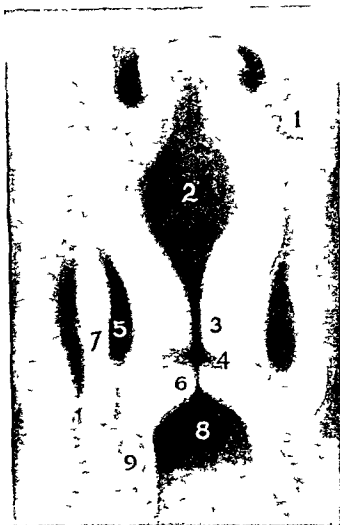


Fig 313—Sketch of a tomogram (laminogram) of a normal adult male showing 1 cross section of the hyoid bone 2 laryngeal ventricle 3 false cords 4 laryngeal ventricle 5 piriform sinus 6 true cord 7 cross section of the thyroid cartilage 8 subglottis and 9 cross section of the cricoid cartilage

**Differential Diagnosis**—*Tuberculous lesions* of the supraglottic area of the larynx may be at times confused with primary carcinomas in this area The tuberculous lesions are usually covered with abundant purulent material and mucus They are usually accompanied by abundant expectoration and in addition they seldom interfere with the normal mobility of the larynx Tuberculous lesions of the larynx are secondary to pulmonary tuberculosis

of respiration. They may be difficult to differentiate from an early, papillary carcinoma of the vocal cord. The biopsy, however, will be conclusive.

Very few conditions of the subglottis can be mistaken for carcinoma. Among these are slowly growing chondromas of the cricoid or tracheal rings, which occur very rarely.

### Treatment

Although a rapid inspection of the medical literature on the subject of the treatment of cancer of the larynx may give the false impression that there is considerable divergence of opinion, this is in part explained by a difference in nomenclature. Actually, there is fundamental agreement on most of the important indications for, and types of, treatment (Table VIII).

TABLE VIII. INDICATIONS FOR TREATMENT AND PROGNOSIS OF CARCINOMA OF THE LARYNX

POINT OF ORIGIN	EXTENSION AND GENERAL CHARACTER	TREATMENT OF CHOICE	PROGNOSIS
Laryngeal wall of epiglottis	Regardless of	Roentgentherapy	Fair
False cord	Regardless of	Roentgentherapy	Good
Ventricle	Regardless of	Roentgentherapy	Fair
Vocal cord	Invasion of laryngeal wall of epiglottis or false cord, very undifferentiated carcinoma is regardless of extension	Roentgentherapy	Fair
	Unlimited to anterior two thirds, cord remaining movable	Roentgentherapy	Good*
	Invasion of anterior commissure and opposite cord	Partial laryngectomy	Very good
		Partial laryngectomy	Good
		Total laryngectomy	Very good
	Extension to entire cord or diminished mobility but no fixation	Roentgentherapy	Good*
		Total laryngectomy	Very good
		Roentgentherapy	Good*
	Extension to subglottic area	Total laryngectomy	Good
Subglottis	Fixation of cord or edema of arytenoid or bulging in piriform sinus	Roentgentherapy	Poor
	Without extension to esophagus	Total laryngectomy	Fair

\*In case of failure a total laryngectomy may be performed

Carcinomas of the *supraglottic area* (laryngeal wall of the epiglottis, false cord, and laryngeal ventricle) are best treated by roentgentherapy. All of these tumors are considered as "extinsic" in the surgical classification. The diagnosis is usually made only after the tumor has become rather voluminous. Often the tumor has insidiously invaded the pre-epiglottic space, or the thyroid cartilage, and the widest excision cannot circumscribe the tumor. Moreover, these carcinomas are commonly undifferentiated, radiosensitive, and radio curable.

In the treatment of carcinoma of the *subglottic area*, a total laryngectomy finds its best indication. These tumors are usually very well differentiated, less radiosensitive, and less radio curable. Although some cases have been cured by means of roentgentherapy, postirradiation recurrences are common. Partial laryngectomies have no place in the treatment of subglottic tumors.

It is in carcinomas of the *vocal cords*, most common of all laryngeal tumors, that there may be differences of opinion as to the treatment. In the early carcinomas of the vocal cord, the choice is between partial laryngectomy and



Fig 315.—Sketch of a tomogram of the larynx in a case of laryngocele showing connection of the air bubble and the ventricle of the larynx with some lateral displacement (From Dr F Leborgne Montevideo Uruguay)

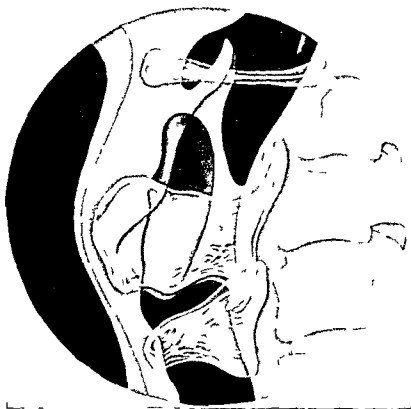


Fig 316.—Sketch of a roentgenogram of the larynx showing unusual well delimited transparent air bubbles superimposed on the areas of the false cord and epiglottis. This should suggest a laryngocele which can be confirmed by a tomogram of the larynx

to be performed. If the patient is very young it is logical that the preference should be given to a conservative procedure. As a rule it has been considered that whichever of these therapeutic procedures is chosen the decision is final. Undoubtedly, however, preservation of life is worth more than any permanent mutilation and to take the responsibility of treating by a conservative procedure which offers a lesser chance of a permanent cure is grave particularly when in case of failure nothing else can be resorted to. But it is perfectly sensible to give the advantages of the conservative procedure when at this time a radical operation is still possible.

Because of the manner in which roentgentherapy has been practiced in the past it has been generally acquiesced that this treatment modifies the tissue of the neck to such an extent that future surgical interventions are prohibited. This is true when therapy is given indiscriminately through excessively large fields and by means of inadequate dosage or poor quality of radiations. Actually carcinomas of the larynx can be treated through small fields and the treatments conducted in such a way as to leave practically no sequelae. When this is done a total laryngectomy can be performed without difficulty for a recurrent carcinoma following roentgentherapy. Harris reported five cases of total laryngectomy following failures by roentgentherapy in which there were no technical difficulties. Cutler reported four additional cases of total laryngectomy in previously irradiated cases without operative or post-operative complications. To these we may add four cases of total laryngectomy being done in each patient approximately a year following roentgentherapy and again without difficulties. Brunschwig also reported on five patients with carcinoma of the larynx in whom a partial laryngectomy was performed following failure of radiation therapy.

**SURGERY**—The surgical treatment of carcinomas of the larynx may be done by a partial or total laryngectomy. Both of these procedures vary technically according to the case and the surgeon. Without intention of describing these surgical procedures in detail we would like to discuss their relative merits and indications.

**Partial Laryngectomy**—These procedures are known also as laryngofissures, thyrotomies and laryngotomies which refer to the method of approach rather than to the type of operation. After opening the larynx through an anterior midline approach a conservative excision of the tumor is done. This usually includes the inner perichondrium of the thyroid cartilage. C. L. Jackson has devised a special variation of partial laryngectomy to be applied to carcinomas of the anterior commissure.

Laryngofissure is most successful in early carcinomas of the anterior two thirds of the vocal cord when there is no extension above or below the cord and when the mobility of the vocal cord has not been hampered.

#### *Contraindications to Partial Laryngectomy*

- 1 Diminished mobility of the cord
- 2 Extension of the tumor to the subglottic or supraglottic area
- 3 Very undifferentiated type of carcinoma

roentgentherapy, and in more advanced cases decision rests between roentgentherapy and total laryngectomy

In considering the treatment applicable to a particular case, several factors must be taken into consideration

*Final Result Offered by the Procedure*—A total laryngectomy for carcinoma of the vocal cord gives the best chance of a permanent cure. A partial laryngectomy in early lesions will offer an appreciable chance of cure, resulting in a subnormal voice and eliminating the disadvantage of a permanent tracheotomy. Roentgentherapy re-establishes the normal physical state and returns the use of a normal voice, but the possibilities of a permanent cure are not as high as those offered by a total laryngectomy. It is obvious that if only the consideration of final results were involved, a total laryngectomy would be the treatment of choice of early as well as advanced carcinomas of the vocal cord, but in practice consideration has to be given to other factors.

*Mutilation and Dysfunction*—A total laryngectomy implies the total loss of voice and the necessity of ultimate readjustments by means of an artificial larynx or the production of a false voice. This has a different significance according to the social status, the age, and the profession of the patient in question, all of which should be weighed before making a decision.

*Histopathology*—The relative advantages of one type of treatment over another may be enhanced by the pathologic features of the tumor to be treated. Efforts have been made to establish a definite correlation between the histologic characteristics of a given tumor and its radiosensitivity. In carcinoma of the larynx, because of its tendency to remain localized, radiosensitivity becomes a very good index of radiocurability. But all that can be said in this respect is that a well differentiated carcinoma is, in general, more curable by surgery and that an undifferentiated carcinoma, no matter how small in appearance, is best treated by roentgentherapy. The intermediate stages between these two extremes are difficult to appraise.

*Mobility*—Indirect laryngoscopic examination will contribute valuable information as to the behavior of the tumor. Fixation or impaired mobility of the different laryngeal structures are important factors to be taken into consideration. Because of the infiltrating nature of some carcinomas and regardless of their histologic features, they rapidly infiltrate the muscles of the larynx and diminish its movements. Others, sometimes voluminous and secondarily infected, never succeed in entirely abolishing the movements of the larynx. Coutard first noticed the importance of this factor and its prognostic value in the course of roentgentherapy. Cutler concluded that the observation of mobility was of greater value than histopathologic study in the choice of treatment of carcinomas of the vocal cord. Obviously those carcinomas which infiltrate the muscle and diminish the mobility of the larynx are not favorable for treatment by roentgentherapy and consequently those which respect the mobility of the laryngeal structures are more favorable for this type of treatment.

*Age and General Condition of the Patient*—The age and general condition of a patient are not of significant importance if a partial laryngectomy is

pharynx, the resonance of the column of air contained in the upper air passages is magnified by means of a mechanical sound box (Fig 317) In some instances this handicap has been dissimulated to such an extent that the difficulty is not noticeable In general, however, the voice produced through an artificial larynx lacks tone and is not always intelligible

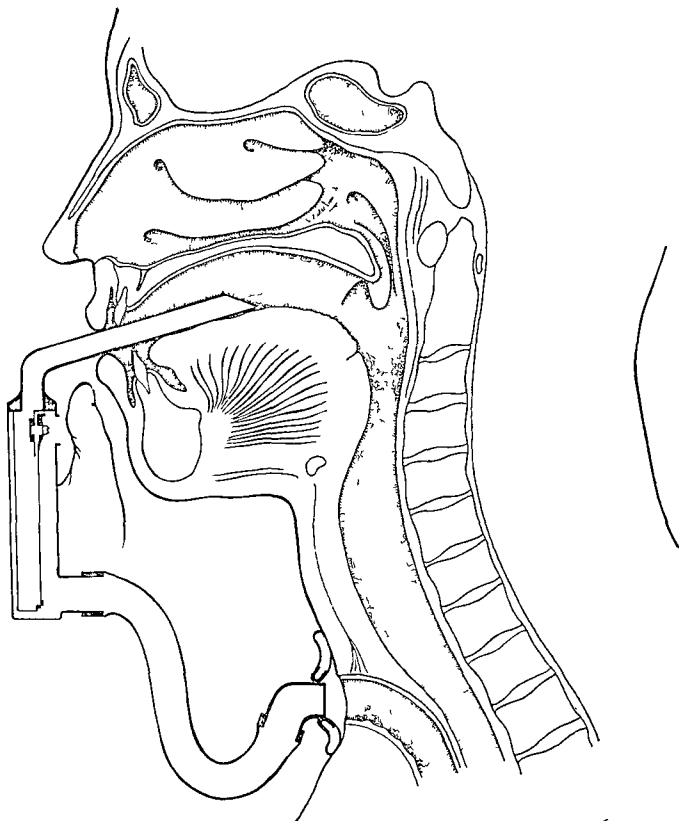


Fig 317—Sketch of an artificial larynx to be used when a total laryngectomy has been done The apparatus projects the air coming from the trachea into the mouth and pharynx The resonance of the column of air contained in the upper air passages is magnified by means of a sound box The patient's thumb is used as an obturator to allow breathing in intervals of speech

**ROENTGENTHERAPY**—The treatment of cancer of the larynx by means of external irradiation is a delicate procedure requiring considerable experience, careful observation, and accuracy Lack of skill in these particular cases spells failure There is an unequalled opportunity in the course of treatment to observe the radiation reactions of the skin, mucous membrane, and underlying vasculo connective tissue through daily examination of these cases This daily consideration is an indispensable part of the treatment which should be adapted to the particular circumstances of the case Complete cure lies between the

C L Jackson reported a series of eighty laryngectomies performed on suitable cases with only one operative death. Patients so operated were able to talk with a varied quality of voice.

A hemilaryngectomy is the most extensive form of partial laryngectomy. Hautant perfected a technique very popular in Europe but seldom practiced in the United States. This type of operation carries a greater mortality risk and most surgeons are of the opinion that a total laryngectomy may be performed with little added hazard and considerably more certainty of a permanent cure.

*Total Laryngectomy*—Variations in the technique of performing a total laryngectomy are mostly devoted to assuring a better healing and elimination of postoperative fistulas. The excision should be large enough to preclude all possibility of local recurrence. As it is sometimes the case with other radical operations applied to the treatment of cancer, total laryngectomy may remove in certain particular cases too much and yet not enough. While most of the laryngeal structures may be removed with ease the tumor is very closely approximated if it has spread posteriorly toward the mouth of the esophagus or anteriorly in the pre epiglottic space.

Total laryngectomy is most satisfactory for tumors of the subglottis and also for very differentiated carcinomas of the vocal cord presenting subglottic extension. In addition the well differentiated carcinomas of the vocal cord extending to its posterior third are in all probability, best treated by this type of operation.

#### *Contraindications to Total Laryngectomy*

1 Undifferentiated tumors of the supraglottic area the operation may not be sufficiently extensive and is often followed by recurrence.

2 Tumors of the vocal cord with invasion or fixation of the arytenoid. When the vocal cord is fixed and the arytenoid is slightly edematous, chances of a successful excision are diminished.

3 Tumors of the vocal cord which although without fixation of the arytenoid, may bulge into the anterior wall of the piriform sinus. The absence of the thyrovertebral "crackle" in these cases should warn against a total laryngectomy.

4 The presence of metastatic adenopathy in the neck.

5 Advanced age and poor general condition of the patient.

The operative mortality for total laryngectomies will vary considerably with the type of lesion treated and the skill of the surgeon. Postoperative pulmonary complications are now less frequent than they used to be. The present average operative mortality is about 10 per cent.

Following a total laryngectomy an intelligible false voice may be produced through coordination of respiration and aerophagia and the production of guttural, lingual, and labial sounds. This pseudovoice, however, lacks variation in pitch and is usually monotonous. The majority of cases require patient adaptation to an artificial larynx which in most instances is quite satisfactory. This apparatus projects the air coming from the trachea into the mouth and



pharynx the resonance of the column of air contained in the upper air passages is magnified by means of a mechanical sound box (Fig 317). In some instances this handicap has been dissimulated to such an extent that the difficulty is not noticeable. In general, however, the voice produced through an artificial larynx lacks tone and is not always intelligible.

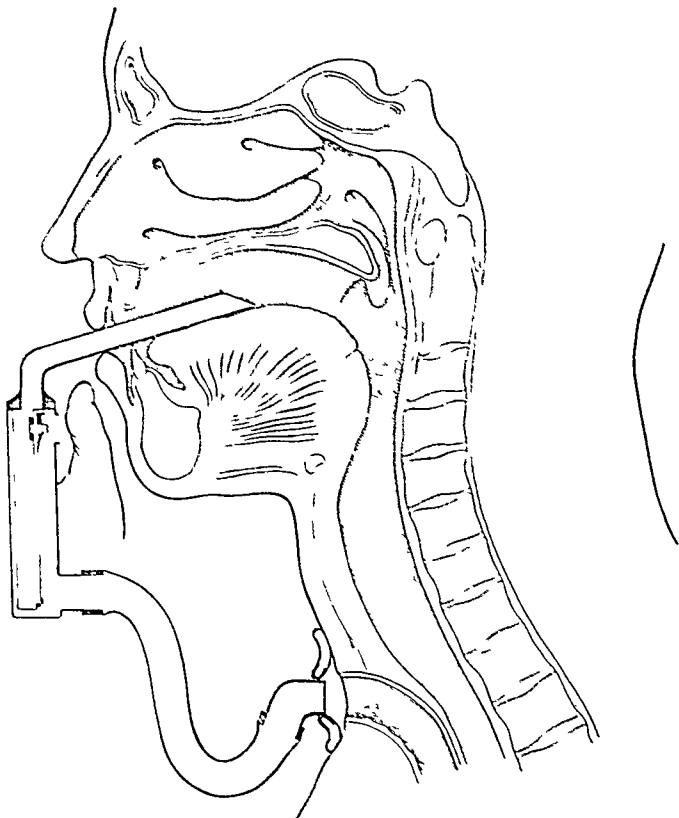


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**ROENTGEN THERAPY**—The treatment of cancer of the larynx by means of external radiation is a delicate procedure requiring considerable experience, careful observation, and accuracy. Lack of skill in these particular cases spells failure. There is an unequalled opportunity in the course of treatment to observe the radiation reactions of the skin, mucous membrane, and underlying vasculo-connective tissue through daily examination of these cases. This daily consideration is an indispensable part of the treatment which should be adapted to the particular circumstances of the case. Complete cure lies between the

narrow limits of enough to excessive irradiation, and it is not sufficient to evaluate the dosage for a given case in a purely arithmetical manner. Clinical control of the treatment is paramount and the daily dosage of radiotherapy must be regulated by the clinical findings. If edema of the larynx appears during the first few days of treatment, the dosage should be changed to avoid untoward reaction of the vasculoconnective tissue. If, on the other hand, this edema is allowed to remain, the radiosensitivity of the tumor will suffer and the treatment may have failed from the start.

It is generally accepted that carcinomas of the larynx should be treated with the best quality of radiation available. This implies the use of at least 200 kv. radiation, high filtration of 1 or 2 mm. of copper, long target skin distance, and as small portals of entry as the topography of the tumor will permit.

Proper evaluation of the extent of the tumor should be done by laryngoscopic and radiographic study. In general, radiographic examination gives a better idea of the projection of the tumor on the superficial tissue of the neck and facilitates the choice of dimensions of the field to be used. The adaptation of the size and shape of the field to the extension of the tumor is not always possible with the use of the metal "cones" of the average equipment. The utilization of the *Regato localizer* described in the chapter on radiotherapy (page 116) will facilitate this adaptation. Diminution in the size of the original portal of entry should be noted during the course of treatment in order to irradiate more intensely the remaining tumor toward the end of treatment. Oversized fields will result in more intense reactions because of the greater production of secondary radiation. The sequelae and the incidence of late necrotic effect are also increased with the use of large fields. When 200 kv. radiation is used two lateral fields are preferable. The use of an anterior field in the midline has not generally been accepted as practical. With higher voltages, however, a single portal of entry will be sufficient in most instances and will facilitate the calculation of depth dosage.

Experience has shown that carcinoma of the larynx should be treated over a period of several weeks. This was demonstrated by Coutard at a time when it was believed that the first condition of success of all radiation treatments was its administration in the shortest time possible. Coutard proved that in the handling of carcinomas of the upper air passages the elongation of treatment facilitated close clinical observation and its adaptation to the particular case. Patients were cured and accidents avoided. This gave birth to the so called *protracted fractional treatment* with which Coutard is credited. In accepting the protraction and fractionation as a sound basis of present radiotherapy, it has too often been forgotten that Coutard's main contribution consisted in the careful, painstaking observation of cases during the course of treatment which placed radiotherapy on a clinical foundation rather than on a purely ballistic one. It was rapidly acknowledged that a greater number of carcinomas of the endolarynx could be cured when the treatments were administered over a period of from four to six weeks. This made the reactions milder and the treatments safer. Consequently, the end results and the palliation of those cases which were not finally cured were considerably more satis-

ervation of mobility Jackson treated seventy-four of these patients by partial laryngectomy Of these, forty-one were well five years or more after treatment, nine died of carcinoma within five years, and five died of intercurrent diseases within five years Nineteen patients were not followed more than one year Not knowing the fate of these last cases, all that can be said is that the five-year cure rate of this procedure is at least between 55 and 75 per cent A total laryngectomy applied to this type of patient will in all probability yield a very high percentage of cures

Most series of patients treated with roentgentherapy include a few early carcinomas of the vocal cord, but the actual possibilities of roentgentherapy in these cases have never been thoroughly evaluated Lenz reported seventeen five-year survivals in a series of forty patients with carcinoma of the vocal cord which he treated by roentgentherapy It can be said without fear of exaggeration that roentgentherapy is highly successful in early carcinomas of the vocal cord with the added advantage that in case of failure the patient may still have the benefits of a total laryngectomy Cutler reported five patients surviving five years after roentgentherapy in seven patients who would have been suitable for laryngofissure Blady reported thirteen of twenty-two patients living and well five years after treatment for carcinoma of the "intrinsic" larynx Cutler reported eighteen of forty seven patients (42 per cent) with carcinoma of the larynx surviving five years after treatment by roentgentherapy from 1938 to 1940 Lenz has made a very detailed analysis of 110 patients with carcinoma of the larynx treated at the Department of Radiotherapy of the Presbyterian Hospital in New York from 1931 to 1941 Thirty patients (27 per cent) were living and well at the end of five years

In a series of 142 patients with carcinoma of the endolarynx treated with roentgentherapy by Coutard, thirty-nine (or 27 per cent) were well and free of disease five years after treatment This group, however, consisted mostly of advanced cases which could not have benefited by any other form of treatment

The results of a total laryngectomy are very variable when applied to the more advanced group of cases Its five-year cure rate may be in the neighborhood of 50 per cent

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main bronchus penetrates the lung at the level of the hilum and, as it extends inward, it grows smaller in size and divides into secondary branches. We use the nomenclature proposed by Jackson and Huber, for each name indicates the position of the branch in any given segment of the lobe. He has identified ten main branches in the right lung and eight in the left lung.

RIGHT LUNG		LEFT LUNG	
<i>lobes</i>	<i>Segments</i>	<i>lobes</i>	<i>Segments</i>
Upper	{ Apical Posterior Anterior	Upper	{ Upper division Lower division (Lingular)
Middle	{ Lateral Medial		{ Apical posterior Anterior Superior Inferior
Lower	{ Superior Medial Basal Anterior Basal Lateral Basal Posterior Basal	Lower	{ Superior Anterior medial Basal Lateral Basal Posterior Basal

The lungs are supplied with blood by the bronchial arteries usually originating in the thoracic aorta and occupying a position posterior to the main bronchi. The branches of the bronchial artery within the lung accompany the divisions and subdivisions of the bronchi, extending to the pulmonary lobules without penetrating them, the bronchial tree within the lobule and the lobule itself are irrigated by the branches of the pulmonary arteries. The venous return of the lungs travels through the pulmonary veins which gather into two main trunks on each side and finally travel to the base of the heart where they open into the left auricle.

**Lymphatics**—The lymphatics of the lungs are a very rich intercommunicating network. The superficial lymphatics of the visceral pleura and the deep lymphatics accompanying the bronchi and pulmonary veins are the most important. There are no lymphatics in the alveoli beyond the ductuli alveolares. The rich plexus of lymphatics accompanying the pulmonary veins becomes more abundant as it flows toward the hilum. These lymphatics communicate with those of the bronchi and pleura. In each lung there are three areas of lymphatic drainage: superior, middle, and inferior (Rouvière).

**Right Lung**—The *superior area* is the anterointernal region of the superior lobe. Its lymphatics are drained by the right laterotracheal lymph nodes and particularly by the large node situated at the arch of the azygos vein. The *middle area* comprises the posteroexternal region of the superior lobe, the middle lobe, and the superior region of the inferior lobe. It is drained by the right laterotracheal and intertracheobronchial lymph nodes. The *inferior area* is formed by the lower region of the inferior lobe and is drained by the lymph nodes at the bifurcation.

**Left Lung**—The *superior area* comprises the upper region of the superior lobe which is drained by the left laterotracheal nodes, the lymph node of the arterial canal, the anterior mediastinal chain of lymph nodes, and the sub-aortic lymph nodes. The *middle area* is formed by the lower region of the superior lobe and the superior and middle regions of the inferior lobe. It is

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## CANCER OF THE LUNG

### Anatomy

The lungs are large cone shaped organs appended to each of the two branches of bifurcation of the trachea. They are separated in the midline by several organs which together are known as the mediastinum.

The lungs are divided externally into lobes by deep oblique fissures extending from above downward and from outside inward. The right lung has an additional transverse fissure and is thus divided into three lobes: an upper middle and lower while the left has only two lobes.

The trachea extends from the cricoid cartilage to the level of the fourth thoracic vertebra where it divides into the right and left main bronchi. Each

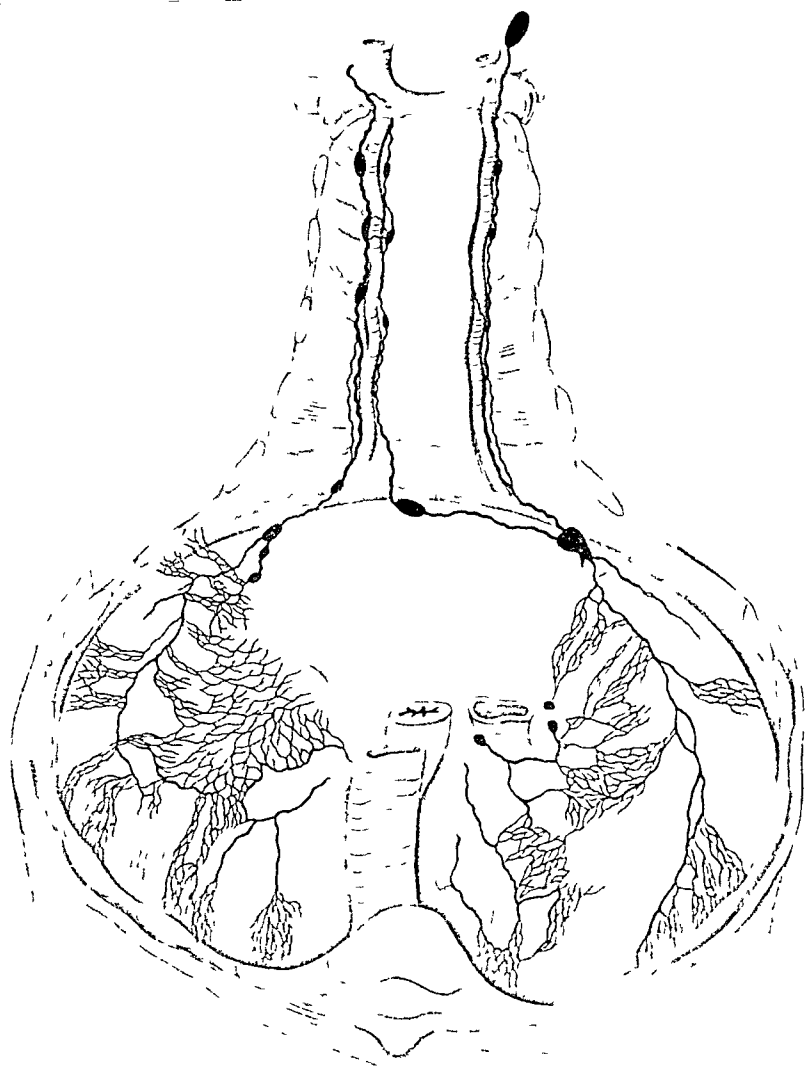


Fig 310—Internal mammary chain of lymphatics and subpleural lymphatics of the diaphragm.  
(After Rouvière)

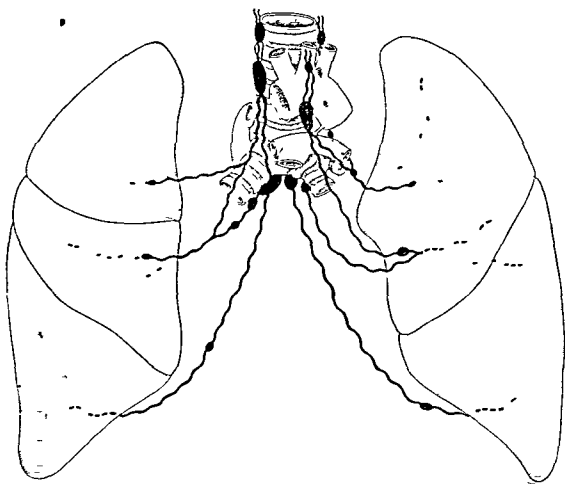


Fig. 318—Schematic representation of the lymphatic drainage of the lung. Note that the lymphatic drainage does not correspond to lobular distribution. (After Rouvière.)



found in patients under 40 years of age and about 60 per cent of them occur in women. Bronchial adenomas however make up a relatively small percent age of all bronchogenic tumors. Of 175 patients with primary tumors of the bronchi seen at the Massachusetts General Hospital 158 had carcinomas and the remaining seventeen had adenomas (Adams, 1945).

There is voluminous literature on the etiology of bronchogenic carcinoma. Most of the causes previously thought to be valid have now been eliminated. Ewing once believed that *tuberculosis* was a pertinent factor in the etiology of carcinoma of the lung but it has since been shown that there is no relationship between the two diseases. Winternitz prophesied an increased incidence of bronchogenic carcinoma due to metaplasia of bronchial epithelium induced during the *influenza* epidemic of 1918. This was not substantiated, for while the incidence of carcinoma rose it showed the same increase in countries which did not have an influenza epidemic (Iceland). *Syphilis* of the lung is a pathologic curiosity and bears no relationship to carcinoma. *Bronchiectasis* has been designated as a cause but in practically every instance in which the two conditions coexist the changes in the bronchi are secondary to lung carcinoma. *Anthracoosis* and *anthracosilicosis* are not related to carcinoma of the lung (Vorwald). Ochsner (1945) believed that *tobacco* was etiologically significant, but in spite of the increase of women smokers there has been no corresponding increase in the incidence of carcinoma of the lung in women.

Carcinoma does occur frequently in *chromate* workers. The mechanism of the action of the chromium compound is unknown. There has been an increased production of chromium and particular attention should be paid to workers in this field. *Asbestosis* may be associated with carcinoma of the lung. The carcinomas may be intimately associated with asbestos bodies and have multiple foci of origin and are often found in a relatively young age group (Lynch). It is worth noting that both chromate and asbestos workers may have symptoms and signs of allergy.

In the cobalt mines of the Schneeberg district in Saxony, Germany and in the uranium mines of Joachimsthal in the Sudetenland the miners have a very high incidence of carcinoma of the lung (Joachimsthal, 50 per cent and over of all workers; Schneeberg 75 per cent and over). The cobalt mine contains large amounts of silica, while the uranium mine does not. The common factor in both mines is a *radioactive matter* which apparently bears a definite relationship to the high incidence of carcinoma of the lung. It has been pointed out that a few years after every discovery of a rich uranium vein a marked increase in the carcinomas of the lungs occurred in the miners. The changes in the blood suggested irradiation anemia (Lorenz). There have been no figures from other mines containing radioactive elements but workers in all such mines should be carefully watched.

### Pathology

**Gross Pathology**—An overwhelming proportion of lung tumors arise within the bronchi (bronchogenic carcinoma, bronchial adenoma), but a few malignant neoplasms arise from alveolar epithelium and pleural mesothelium.

drained by nodes in the anterior mediastinal and laterotracheal chains and also by the nodes at the bifurcation. The *inferior area* comprises the lower region of the inferior lobe and is drained by the lymph nodes at the bifurcation.

The lymphatics of the *parietal pleura* can be divided into those of the diaphragm and those of the thoracic wall. The collecting trunks of the lymphatics of the diaphragm empty into the lateral precardiac and anterior mediastinal lymph nodes on the left and posterior mediastinal lymph nodes on the right. The collecting trunks of the posterior region of the diaphragm communicate with the rich network of subperitoneal infradiaphragmatic lymphatics which terminate in intra abdominal para aortic nodes. They are also in communication with the lymphatics of the liver, the adipose capsule of the kidney, and the suprarenal gland. The lymphatics of the thoracic pleura are divided by Rouviere into three regions. First, those of the first costal arch, first intercostal space, and entire pleural dome which are drained by the lymph nodes of the transverse cervical and internal jugular chains. They may also drain into a subclavian or mediastinal trunk. At times some of these collecting trunks may terminate in the upper axillary nodes. Second those located between the second and fourth ribs which are drained by the lymph nodes of the posterior intercostal and internal mammary chains but some may occasionally end in axillary lymph nodes. Third those extending from the fourth to the sixth rib. The collecting trunks of this region may also empty into axillary lymph nodes.

### Incidence and Etiology

The reported incidence of carcinoma of the lung has risen rapidly over the last twenty year period. This increase has been steadily progressing since the year 1920 while the incidence of carcinoma of the stomach, uterus, and skin has remained the same. Autopsy statistics have also shown increases in bronchogenic carcinoma and the statistics from many large centers show that carcinoma of the lung varies from first to fourth as a cause of death from malignant tumors. In centers with highly qualified thoracic surgeons, a concentration of cases of bronchogenic carcinoma occurs so that the figures tend to give an erroneous impression. The use of more refined diagnostic measures such as roentgenography, radioscopy, tomography, and bronchoscopy have aided the early and more frequent diagnosis of carcinoma of the lung. Because it is found primarily in older age groups and as the number of people reaching the upper decades has increased, the incidence of carcinoma of the lung has correspondingly increased. It is considered however that a respectable proportion of the increase in carcinoma of the lung is real rather than due to improved methods of diagnosis and increased recognition (Simons Llambe).

Cancer of the lung is primarily a disease of males (10 to 15 per cent females). Lipidermoid carcinoma and very undifferentiated carcinomas are almost exclusively found in men, while about one third of the cases of adenocarcinoma occur in women (Adams, 1946). There seems to be no difference in the incidence of cancer of the lung in Caucasian and Negro races (Martinez). The peak age incidence is between 50 and 59 years. About four fifths of all carcinomas of the lung occur between the ages of 40 and 70 years. By contrast, bronchial adenomas occur in younger individuals about 70 per cent are

well delineated and at times yellow in color and present areas of hemorrhage. Their local invasive qualities are the most prominent sign of malignancy. As they are mainly extrabronchial, they grow around bronchial cartilages and at

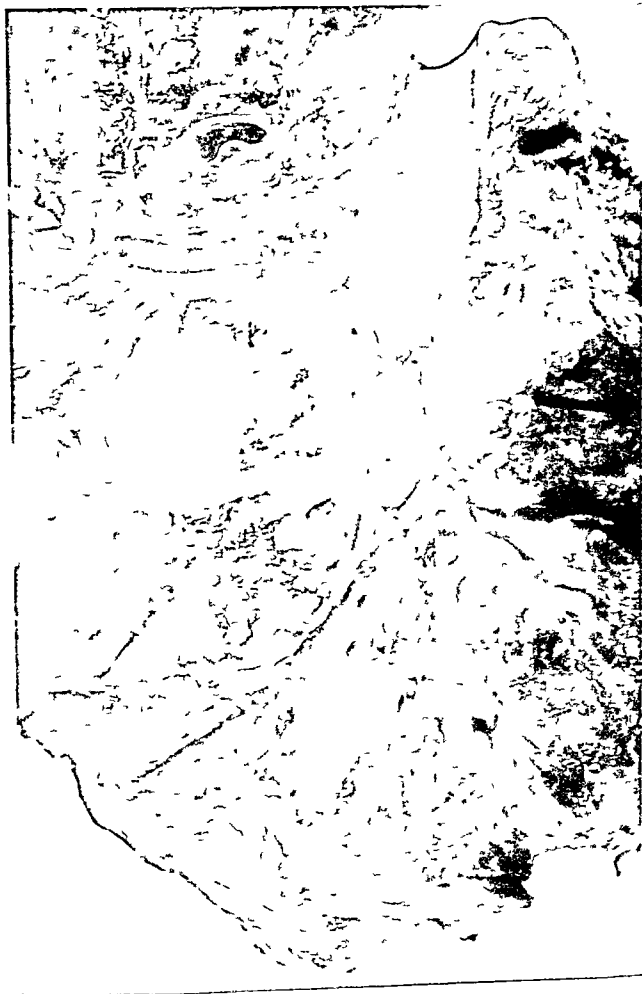


Fig 320—Typical epidermoid carcinoma arising from main stem bronchus with involvement of hilar lymph nodes and direct spread into the adjoining lung

times destroy them. They may extend so deeply that regional lymph nodes are directly invaded. It is not rare, however, for tumor to grow around these nodes, leaving them free from tumor. With further increase in size, the tumors break into the lung parenchyma where they generally remain localized. They may

*Bronchogenic carcinoma* is found more frequently in the right (60 per cent) than in the left lung. It arises in the major bronchus in about 75 per cent of the cases, and in one of the peripheral bronchi in about 25 per cent. Tumors exhibiting definite squamous characteristics uniformly ulcerate the bronchi, while those arranged in the form of acini tend to invade and constrict the bronchi often without ulceration. The squamous carcinoma may remain fairly well localized and areas of keratinization can be seen as small granular like areas. Variable degrees of bronchial ulceration are seen. The more undifferentiated carcinomas are often large and can even replace an entire lobe of the lung. In these large tumors, areas of hemorrhage and necrosis are frequent. The adenocarcinomas can also be large and may at times show areas of mucoid degeneration.

Bronchogenic carcinomas tend to develop submucosal extension along the bronchi, but this extension often cannot be seen (Fig 324). As the tumor grows within a major bronchus, it insinuates itself between and eventually destroys the bronchial cartilages (Fig 320). With further extension it may even reach the visceral pleura, grow through it and become adherent to the thoracic wall or diaphragm. On the left, the tumor can spread to involve the pericardium and in rare instances the myocardium. Rarely carcinomas of the lung may spread through the chest wall to form an ulcerating mass on the skin. In this local spread various nerves may be compressed or invaded (vagus recurrent laryngeal phrenic, sympathetic, and cervical ganglion nerves). Other mediastinal structures such as pulmonary vessels can be surrounded, but usually the arteries are invaded only in their adventitial portion. Not too rarely, the tumor compresses the superior vena cava and partially or wholly obstructs it. True thrombosis is rare (Hussey). Occlusion of major bronchi either partial or complete often results in atelectasis and infection distal to the tumor. This infectious process may take the form of a diffuse necrotizing bronchopneumonia which may secondarily perforate the pleura to cause empyema. In other instances the obstruction may initiate the formation of a lung abscess localized to a single lobe.

There is no doubt that *bronchial adenoma* is to some extent, a misnomer, for these tumors do locally extend, can metastasize to regional lymph nodes and even upon rare occasions to distant organs such as the liver (Anderson). They, however, behave clinically in an entirely different fashion from bronchogenic carcinomas. They are very slowly growing and Womack, Graham Weller, Alexander, and Haight believe that the best way to classify them is to call them Grade I carcinomas. They certainly should be separated when groups of carcinomas treated surgically are reported.

Bronchial adenomas arise in the main stem bronchi. They are soft and well vascularized and are frequently associated with abnormal lobulations of the lung and abnormalities in the bronchial division (Womack). They can grow mainly within the bronchus (rarely) or they assume a dumbbell shape (Fig 327) with about half of the tumor growing within the lumen (fairly common) or they can be mainly extrabronchial (most common). These tumors may become superficially ulcerated within the lumen (Fig 325). On section they are usually very

well outlined and at times yellow in color and present areas of hemorrhage. These blood-invasive qualities are the most prominent sign of malignancy. As they are mainly extrabronchial they grow around bronchial cartilages and at



Fig. 323—Typical of dermoid carcinoma arising from main stem bronchus with involvement of hilar lymph nodes and direct spread into the adjoining lung.

times destroy them. They may extend so deeply that regional lymph nodes are directly invaded. It is not rare, however, for tumor to grow around these nodes, leaving them free from tumor. With further increase in size the tumors break into the lung parenchyma where they generally remain localized. They may

invade the submucosa for a short distance (Foster Carter) and rarely may extend directly into mediastinal lymph nodes (Churchill)

In the rare carcinomas of the lung, which arise from the *alveolar epithelium*, the lungs are studded with nodules up to 2 cm in diameter. These nodules are yellowish gray in color and firm and at times fuse to form larger masses. With further growth, large areas of lung parenchyma are replaced. Very rarely there may be a diffuse involvement of one or both lungs, which may simulate lobar pneumonia.

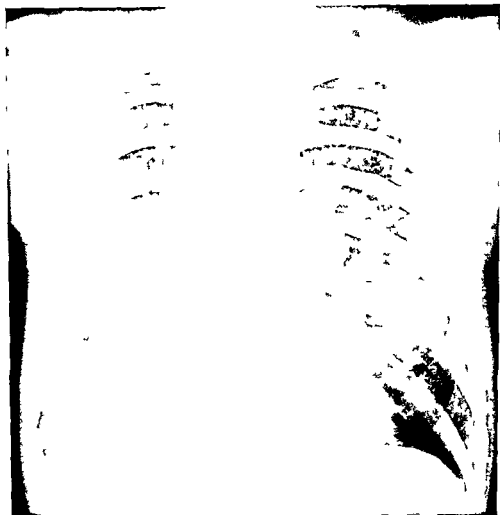


Fig. 371—Roentgenogram of the case illustrated in Fig. 370 showing atelectasis. A considerable portion of the triangular shadow extending from the right hilum represents secondary inflammatory changes rather than carcinoma.

The *pleural mesothelioma* is a very definite but rare tumor arising from the pleura and it may be localized or diffuse. Early the pleura is markedly thickened, and yellowish gray. The tumor has variable speeds of growth, but eventually pleural fluid forms at first yellow but later bloody. As the tumor becomes more diffuse it may affect the entire pleura on one side, invade locally between the fissures, cross the mediastinum and even involve the pleura

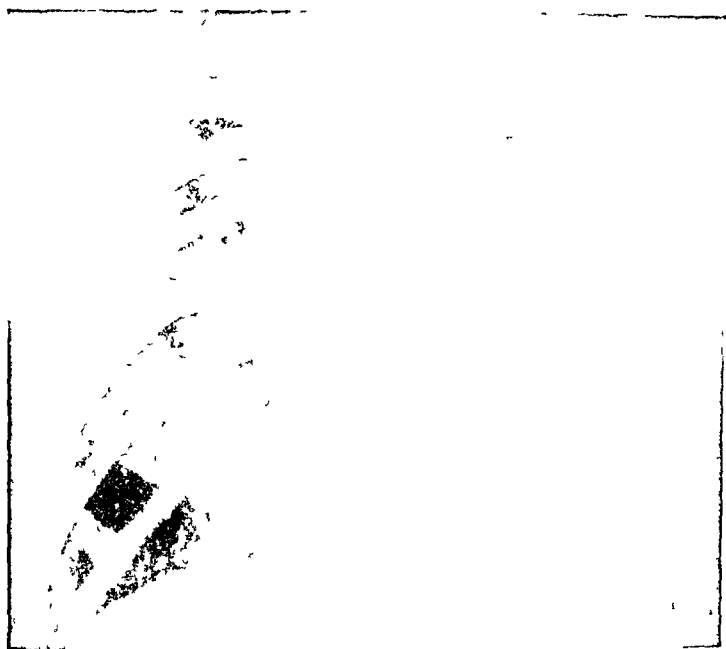


Fig 322—Roentgenogram of the case illustrated in Fig. 321. Note homogeneous shadow obliterating the left apex. Rib destruction could be visualized by bone density films.

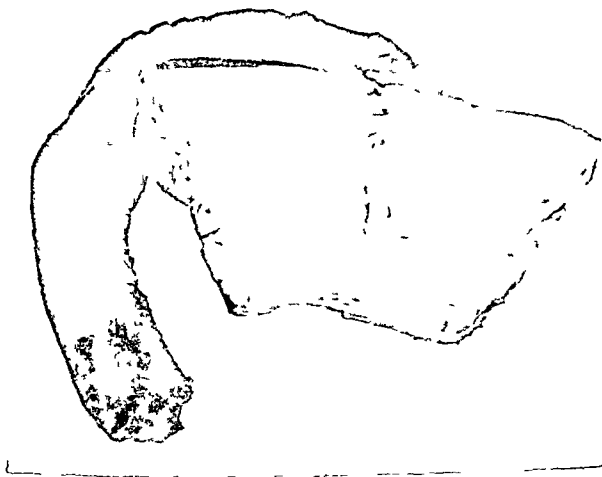


Fig 323—Bronchogenic carcinoma of the thoracic outlet (Pancoast syndrome). This tumor arose from a peripheral branch bronchus to destroy rib, involve nerve and cause a Horner's syndrome.

invade the submucosa for a short distance (Foster Carter) and rarely may extend directly into mediastinal lymph nodes (Churchill)

In the rare carcinomas of the lung which arise from the *alveolar epithelium*, the lungs are studded with nodules up to 2 cm in diameter. These nodules are yellowish gray in color and firm and at times fuse to form larger masses. With further growth, large areas of lung parenchyma are replaced. Very rarely there may be a diffuse involvement of one or both lungs, which may simulate lobar pneumonia.



Fig. 321—Roentgenogram of the case illustrated in Fig. 320 showing atelectasis. A considerable portion of the triangular shadow extending from the right hilum represents secondary inflammatory changes rather than carcinoma.

The *pleural mesothelioma* is a very definite but rare tumor arising from the pleura, and it may be localized or diffuse. Early, the pleura is markedly thickened, and yellowish gray. The tumor has variable speeds of growth, but eventually pleural fluid forms at first yellow but later bloody. As the tumor becomes more diffuse it may affect the entire pleura on one side, invade locally between the fissures, cross the mediastinum, and even involve the pleura



Fig 325

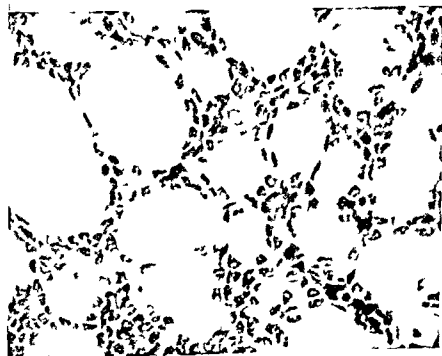
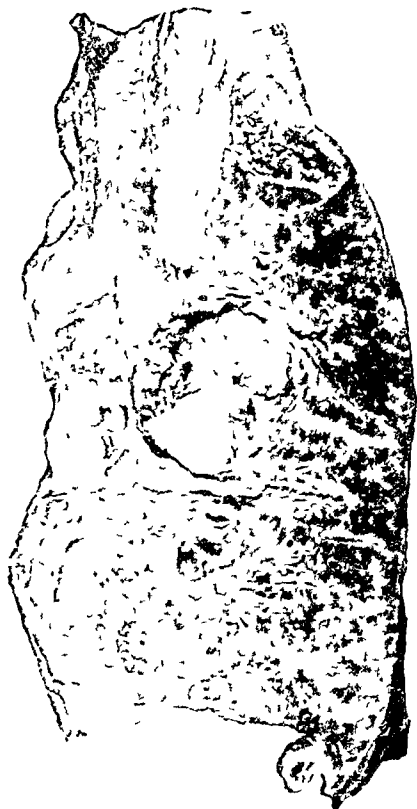


Fig 326

Fig 325.—Gross specimen of a large circumscribed superficially ulcerated bronchial adenoma involving a main stem bronchus. Note the multiple small areas of destruction distal to the occluded bronchus. This patient died of pulmonary infection with the tumor still localized.

Fig 326.—Photomicrograph of a bronchial adenoma. This is the angiomatoid type of tumor with prominent vascularization. Note absence of mitotic figures.

of the opposite side. In some instances tumor invades the diaphragm, pericardium, thoracic wall, and even peritoneum.

**METASTATIC SPREAD**—The profuse lymphatic network, the great vascularity, and the constant respiratory movements of lungs and bronchi tend to facilitate the spread of bronchogenic carcinomas. The lymphatic spread is the most common, and involvement of mediastinal peritracheal lymph nodes almost always takes place (Fig. 329). It is not rare for the microscopic examination to show tumor plugging the lymphatics of the lung itself and pleura. The lymphatic spread becomes more extensive when pleural adhesions form and more distant pathways of dissemination become available. With an adherent pleura the tumor can terminate in the axillary lymph nodes (Fig. 331). With



Fig. 34.—Photomicrograph demonstrating an undifferentiated epidermoid carcinoma growing beneath the intact overlying columnar ciliated epithelium of the bronchus (moderate enlargement).

diaphragmatic adhesions, lymph nodes in the anterior and posterior mediastinum and prepericardiac nodes can become involved (Fig. 330). The tumor can also travel via the lymphatics through the diaphragm and involve nodes in the region of the kidney, along the aorta, and near the terminal portion of the esophagus (Fig. 332). If tumor grows into the pulmonary veins, systemic dissemination becomes inevitable and brain, bone, suprarenals, and liver become the site of metastases. The tumor can also reach the brain by way of the posterior bronchial veins and the vertebral plexus. The frequency of metastases is related to the degree of differentiation of the tumor. The extremely well differentiated squamous carcinomas may remain localized for long periods of time and metastasize only to regional lymph nodes (Goldman).

Olson twenty-nine squamous-cell carcinomas (42 per cent), seventeen adenocarcinomas (24 per cent), and twenty-three undifferentiated carcinomas (33 per cent)

The *bronchial adenoma* has very characteristic features and is often covered by an intact bronchial mucous membrane which may become stratified squamous in character. Beneath the epithelium the extremely well-vascularized tumor has an appearance suggesting fetal lung. The epithelial cells of the tumor are uniformly regular and mitotic figures are infrequent (Fig 326)

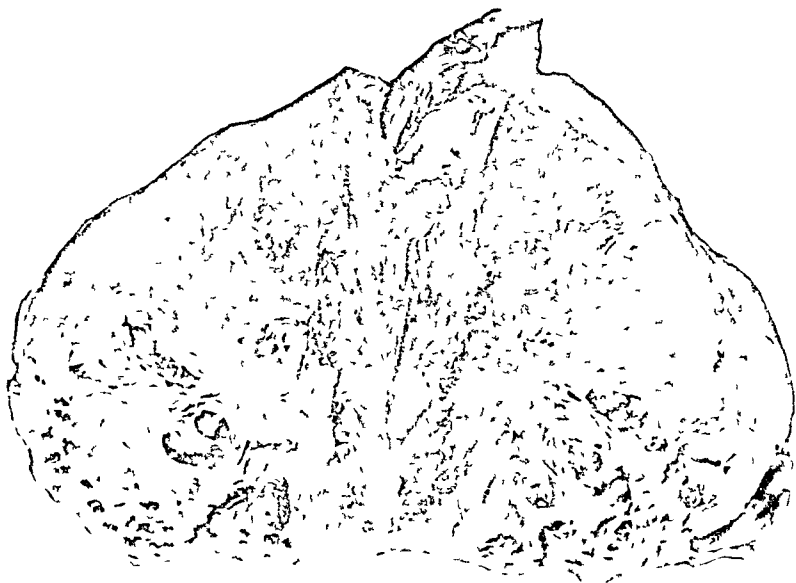


Fig 328—Gross photograph of a lower lobe of lung with multiple abscess cavities secondary to an occluding bronchial adenoma. These inflammatory changes dominated the clinical picture. (Courtesy of Dr Robert Moore, Department of Pathology, Washington University School of Medicine, St. Louis, Mo.)

The pattern of the tumor may or may not be uniform and individual types are described as alveolar, medullary, or angiomatoid in character. Bone and cartilage (fragments of bronchial cartilage or bone due to metaplasia of the stroma) may be present. The cell origin of this tumor is still a matter of conjecture. Womack and Graham believe that they arise from endoderm and mesoderm and should therefore be designated as mixed tumors. The mucous glands, ducts, and an individual cell designated as the oncoocyte (Stout) have been suggested as possible points of origin.

The *alveolar carcinoma* arises from the cells lining the alveolar walls. The tumor cells can be seen attached to the alveolar wall by very delicate connective tissue. The cells are cuboid or columnar, and papillary projections

The true so called *bronchial adenoma* remains well localized and its effects are due to local spread, not to distant metastases. Anderson reported one case of bronchial adenoma with a single large metastasis in the liver. Womack and Graham believe that distant metastases are not infrequent.

The *alveolar cell carcinoma* may have no metastases but most commonly it spreads to the regional hilar lymph nodes. Infrequently metastases to distant lymph nodes, liver, suprarenals and brain can occur.

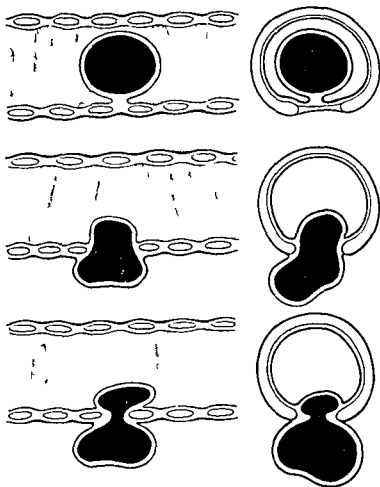


Fig. 377—Schematic representation of the three morphologic types of bronchial adenoma: endobronchial intramural and extrabronchial. (From Brunn, H. and Goldman, A. Surg. Gynec. & Obst. 1940.)

In approximately one half of the cases of *pleural mesothelioma* there are no metastases. About 25 per cent involve hilar and bronchial lymph nodes only, and the remaining 25 per cent metastasize particularly to liver, distant lymph nodes, kidneys, brain, suprarenal glands, and pericardium (Neuburger).

**Microscopic Pathology**—*Bronchogenic carcinoma* is usually divided into three groups—squamous cell carcinoma, adenocarcinoma, and undifferentiated carcinoma. Many workers believe that no matter what the pattern of the tumor, it has an origin from a single multipotential cell in the bronchial wall. This cell can form mucous glands, squamous epithelium, or other cellular components. The proportion of these particular cellular types was reported by

### Clinical Evolution

The evolution of *bronchogenic carcinoma* has a variable speed. The earliest symptom is usually an irritative cough accompanied by increased amounts of mucoid secretion. This is followed by signs of bronchial obstruction with or without infection. With further growth of the tumor the sputum may be tinged with blood. Unilateral wheezing occurs when air becomes trapped by a ball-valve action (Fig 333). The involved lobe becomes distended, and, if there is complete obstruction, atelectasis takes place with resulting dyspnea. The cough may become more acute and be accompanied by chest pain. Hemoptysis occurs rather frequently but usually is not profuse. With partial bronchial block it is not unusual for symptoms of infection to become apparent, often suggesting influenza or pneumonia. With decrease of the bronchial obstruction, the symptoms of bronchial infection may disappear. At times an abscess developing secondary to the carcinoma (Fig 336) may increase rapidly in size, perforate through the pleura, and cause empyema.

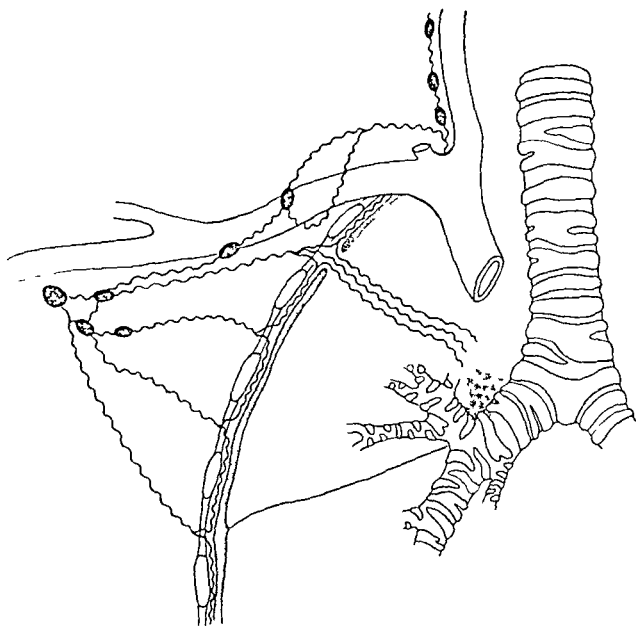


FIG. 331.—Anatomic sketch showing the pathway to axillary metastases from a bronchogenic carcinoma after pleural symphysis.

When the carcinoma spreads to involve the sympathetic chain, a Horner's syndrome may develop. With a so-called superior pulmonary sulcus tumor, there may be excruciating pain radiating down the arm of the involved side as well as considerable local pain. When the tumor involves the phrenic nerve, increased dyspnea may result from a paralyzed leaf of diaphragm.

are common. Cilia are not present. Tumor cells are often seen within the lymphatics. In the immediate vicinity of the tumor, fibrosis, chronic pneumonia, atelectasis, and emphysema are not infrequent (Neuburger).

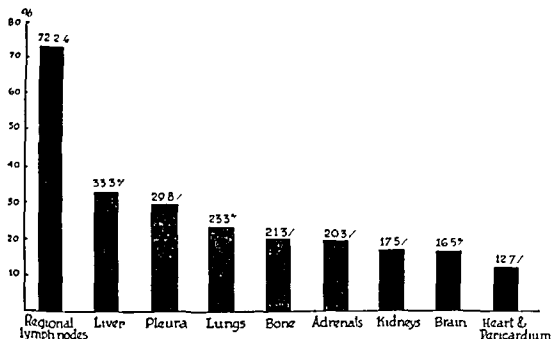


Fig 329—Incidence of metastases in 3017 collected cases of carcinoma of the lung (From Ochsner A. J. Thoracic Surg. 1942)

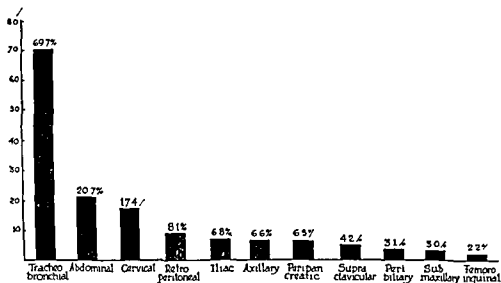


Fig 330—Relative distribution of lymph node metastases in 1708 collected cases of carcinoma of the lung. Note high proportion of abdominal metastases (From Ochsner A. J. Thoracic Surg. 1942)

The *pleural mesotheliomas* have a variable microscopic picture and are usually made up of epithelial elements and fibrous stroma. At times the growth appears to lack epithelioid elements and suggests a fibrosarcoma. The histogenesis is somewhat uncertain. Tissue culture has shown a probable origin from mesothelium (Murray, 1942).

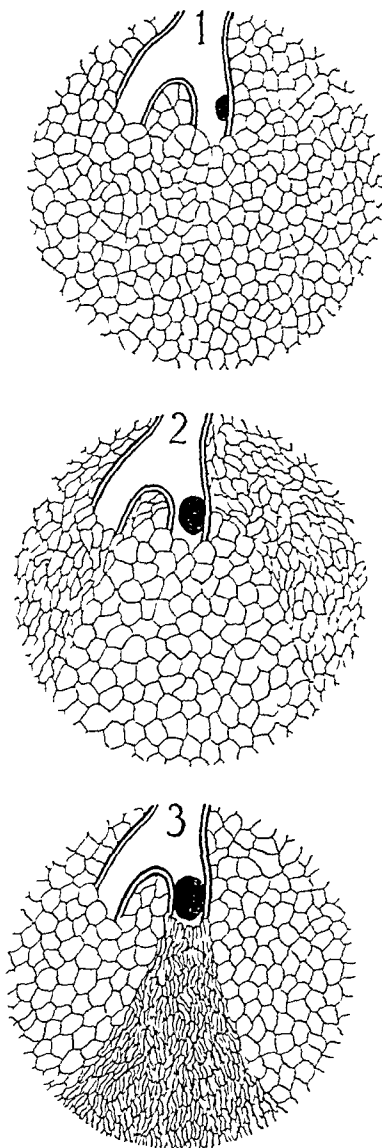


Fig 333 —Schematic representation of the mechanism of bronchial obstruction by tumor developing in the bronchial lumen 1, no obstruction no change in peripheral lung; 2, ball valve action emphysema distal to partial obstruction; 3, complete obstruction distal atelectasis

Peripheral bronchogenic carcinomas make up approximately 25 per cent of all bronchogenic carcinomas and may reach a large size before any clinical symptoms such as cough, pleural pain or hemoptysis appear (Thornton). Because of their rapid centripetal growth, the blood supply may be centrally impaired, causing necrosis liquefaction and central rarefaction.

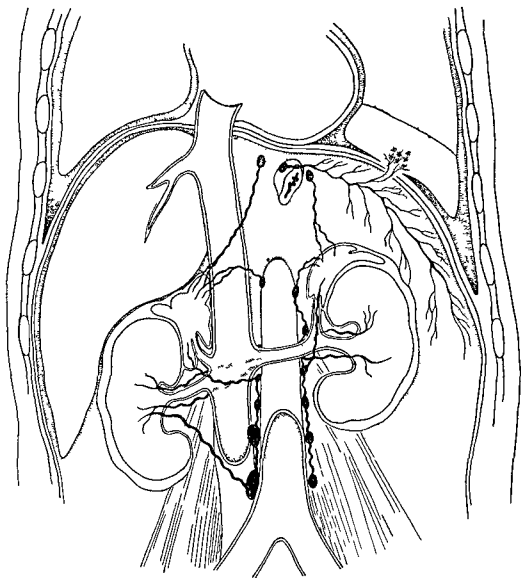


Fig. 33°—Anatomic sketch to illustrate the pathways to abdominal metastases from carcinoma of the lung after fusion of the visceral and parietal pleura of the lower lobe.

Bronchogenic carcinomas not infrequently metastasize to the brain and the dominating symptoms may strongly simulate a primary brain tumor. This is particularly true in primary bronchogenic tumor without bronchial obstruction. Addison's disease rarely occurs when there is secondary involvement of both suprarenal glands. The first symptom of a carcinoma of the lung may be caused by bone metastases with pain in the chest and lumbar region. The symptomatology in 157 cases tabulated by Adams is shown in Table IX.



the chest wall to form an ulcerating mass. A carcinoma involving the thoracic inlet may present a Horner's syndrome (miosis, enophthalmos, and narrowed palpebral fissure), and there may be neurological changes in the arm on the involved side. Metastases are often evidenced by enlarged supraclavicular nodes and a nodular liver.

It is important to know whether a bronchogenic tumor represents a so-called bronchial adenoma or a bronchogenic carcinoma. In most instances a biopsy is the determining factor. The sex of the patient, the duration of the disease and the bronchoscopic observations are the most important differential points (Table X).

TABLE X DIFFERENTIAL CHARACTERISTICS OF BRONCHOGENIC CARCINOMAS AND BRONCHIAL ADENOMAS

	BRONCHOGENIC CARCINOMA	BRONCHIAL ADENOMA
Sex	90% male	60% female
Age	10% before 40	70% before 40
Duration—1 year plus	2%	90%
5 years plus	0	80%
Metastases	Very frequent	Practically never
Brain pathology	Metastases frequent	Abscess may occur
Hemoptysis	10%	80% (often repeated)
Pain	Often present	Frequently absent
Bronchoscopic observation	Often fixed, ulcerated, crusting, widened, mediastinum fixed	Usually nonulcerated, bleeds easily, no fixation of mediastinum
Operability	Low	High

Bronchogenic carcinoma frequently suggests an unresolved pneumonia. The roentgenologic picture may change almost daily according to the degree of bronchial block and infection. Should the patient expectorate a portion of the tumor, the bronchial drainage improves, and the next roentgenogram shows a clearing of the pulmonary process, this evolution may be interpreted as improvement of a pneumonic process. *Any peculiar or poorly explained pneumonic process which demonstrates an unusual clinical and roentgenologic behavior in the lungs of an older individual should be suspected of being bronchogenic carcinoma.* If a lung abscess is diagnosed roentgenographically in the absence of a clear-cut etiology, there may very well be a primary carcinomatous obstruction in a main stem bronchus, particularly if it occurs in an elderly male. If the abscess spreads to the pleural cavity, rupture may ensue and cause empyema and massive infection. This may lead to vigorous treatment of the infection while the primary cause is overlooked. A similar clinical picture can occur in bronchial adenoma.

Bronchogenic carcinoma frequently metastasizes to the brain and there is probably no prominent neurosurgeon in the country who has not explored the brain for a lesion thought to be primary but which turned out to be metastatic from an occult carcinoma of the lung. A roentgenologic examination of the chest should therefore be done routinely for every suspected primary brain tumor (Parker).

Bronchogenic carcinoma very frequently metastasizes to the suprarenal glands and may rarely cause a syndrome of Addison's disease. Bronchogenic

TABLE IX SYMPTOMS IN 107 PATIENTS WITH CARCINOMA OF LUNG  
(From Adams 1 J A M A 1946)

	CASES	PER CENT
Cough	146	93
Pain	85	54
Expectoration	83	53
Hemoptysis	69	44
Wheeze	22	14

In the late stages of the disease and caused primarily by pulmonary infection there may be marked weight loss, secondary anemia, and prominent cardiorespiratory symptoms. Death may occur from widespread dissemination of the disease but much more frequently is due to cardiorespiratory failure.

Bronchial adenomas develop very slowly and because of their extreme vascularity the first symptom is often hemoptysis. Symptoms due to bronchial obstruction may occur sometimes associated with repeated respiratory infections. As the tumor grows there may be profuse hemorrhages. With an almost complete obstruction an atelectasis may develop and result in dyspnea and other physical signs. Infection however is the most common complicating factor and gives symptoms suggesting influenza and atypical pneumonia. The symptoms vary in accordance with the degree of bronchial block.

The infection which may be associated with lung abscess (Fig 328) is sometimes sufficient to cause death if there is no surgical interference. A brain abscess may also develop terminally.

The clinical evolution of *alveolar carcinomas* is variable but it is usually rapid. The patients have cough and bloody sputum. Because of the extensiveness of the often bilateral disease cyanosis and dyspnea are frequent. When the pleura is involved pain, pleural effusion, and marked dyspnea result. The patients do not survive more than a year. Death occurs from pulmonary insufficiency.

The growth rate of a *pleural mesothelioma* is often slow. The first sign may be the development of a small effusion which gradually increases. With more fluid dyspnea appears. This gradual process may take several years. With spread of the tumor to the mediastinum and opposite pleura dyspnea becomes extreme and death occurs from pulmonary insufficiency.

### Diagnosis

**Clinical Examination**—The clinical examination of a patient with an early cancer of the lung or a bronchial adenoma arising in a main stem bronchus often yields very few positive findings. However, the early signs and symptoms are related in most cases to variable degrees of bronchial block. There may be unilateral wheezing, and air may become trapped and there are zones of hyperresonance distal to the block. If atelectasis occurs because of complete bronchial block the trachea may be deviated to the affected side, there is dullness over the involved lobe or lobes and the heart is also deviated to the same side. After a bronchogenic carcinoma is no longer localized there are signs and symptoms of extension or metastases. Local spread to the pleura is shown by pleural effusion. Very rarely the tumor may ulcerate through

metastatic carcinoma. The roentgenologic picture of a *pleural mesothelioma* is usually not diagnostic, for the changes present are those of thickened pleura with effusion.

### Methods of Obtaining Tissue for Diagnosis —

*Bronchoscopy*—This extremely important diagnostic measure is mandatory for every patient suspected of having a bronchogenic tumor. With a skilled operator, the patient suffers little discomfort, but the recognition of the various bronchial lesions requires relatively long experience. Most bronchial adenomas are recognized at bronchoscopy. Biopsy may cause considerable bleeding because of the rich vascularity, but these tumors usually heal

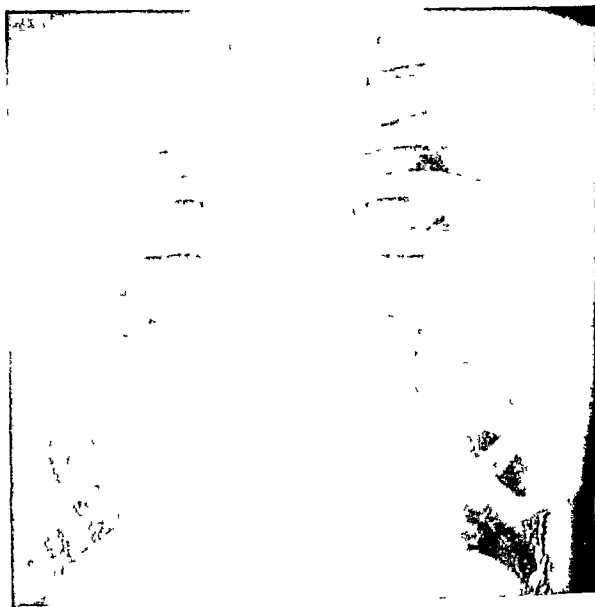


Fig 334—Roentgenogram of a bronchogenic carcinoma with complete atelectasis of the right upper lobe. This patient was found to be operable on exploratory thoracotomy. (Courtesy of Dr C. A. Brashear, Missouri State Sanatorium, Mount Vernon, Mo.)

quickly and the epithelium grows over the defect. In bronchogenic carcinoma, biopsy is an adequate diagnostic measure in 40 to 75 per cent of the cases. In the early cases the biopsy may more often fail to make the diagnosis (Overholt, 1946), and several attempts may be necessary before adequate material is obtained. If a tumor casts a circular shadow on the roentgenogram, it invariably designates a peripheral lesion, and it therefore cannot be visualized at bronchoscopy (Adams, 1946).

*Examination of Cells From the Sputum and Bronchoscopic Aspiration*—The identification of neoplastic cells in sputum is sometimes difficult because of disintegration. Herbut examined material obtained at bronchoscopy from

carcinomas rather frequently compress the superior vena cava, and the resulting signs and symptoms have been summarized by Ochsner (1936) as follows

- 1 1 dema and edema of the face, neck, and upper extremities (aggravated by assuming the horizontal position and relieved when erect)
- 2 Venous hypertension in arms
- 3 Normal venous pressure of lower extremities
- 4 Development of subsequent varicosities on anterior thorax
- 5 Development of deep collateral vessels

**Roentgenologic Examination**—The roentgenologic examination of the chest in patients with *bronchial adenoma* and *bronchogenic carcinoma* is of paramount importance. The abnormalities observed are often caused by variable degrees of bronchial block and infection, and the picture may be bizarre and ever changing. There is no doubt that a detailed consideration of the roentgenologic appearance of a segmental collapse of the lung with radioscopy and roentgenograms taken at various angles materially heightens the percentage of correct diagnoses (Robbins, Foster Carter).

If the tumor originates in the main stem bronchus, the first roentgenologic change is an emphysema of the involved lobe due to trapping of air. As the tumor further obstructs the bronchus, atelectasis may appear (Fig 321) but the roentgenologic signs depend upon the lobe involved. The lateral and oblique roentgenograms often localize the area of atelectasis. The shadow peripheral to the lung block may also be prominent, and in many instances the changes present are due to infection rather than to tumor. Not too rarely the roentgenologic picture reveals lung abscess secondary to a proximal block of the bronchus. In other instances the tumor may arise near the apex of the lung showing an area of homogeneous increased density with a narrowing of the rib spaces (Fig 322). With bone density films, underlying destruction of the ribs may be depicted. If the tumor is associated with pleural effusion or any degree of thickening of the overlying pleura, it may be necessary to take overexposed films in order to reveal underlying pathology.

The areas of bronchial block may be clearly shown by lipiodol studies (García Capurro). If lipiodol studies are used, the technique of bronchography outlined by Adams and Davenport is very useful. Planigraphy is of great value in locating bronchogenic tumors, but the procedure takes considerable technical skill and experience in interpretation. It can indicate, however, whether tumor is growing out into the parenchyma. Frimann Dahl believes that further use of this measure will almost eliminate the use of bronchography with lipiodol. If lipiodol becomes trapped by an area of obstruction a pneumonitis may develop and delay surgical treatment for several weeks.

Metastatic bone lesions are usually osteolytic and it is not rare to see a portion of a rib completely destroyed by tumor. In other instances the vertebrae and skull may contain areas of osteolytic destruction.

The roentgenologic examination of an *alveolar carcinoma* of the lung often reveals bilateral well defined nodules with or without pleural effusion. The hilar nodes may be enlarged. These changes are commonly interpreted as

often bloody because of involvement of the pleura by bronchogenic carcinoma, alveolar carcinoma, or pleural mesothelioma

**Aspiration Biopsy**—One-fourth to one-half of the cases of bronchogenic carcinoma cannot be biopsied through the bronchoscope. When these tumors are located peripherally, aspiration biopsy under radioscopic often procures enough tissue for diagnosis. If the tumor is located close to the hilum, this procedure is not indicated. We have never encountered any complications from aspiration biopsy nor have we seen implantation of tumor in the needle tract. In certain instances a peripherally placed lesion may be thought to be a bronchogenic carcinoma, but aspiration biopsy may show a benign tumor such as neurofibroma, a metastatic carcinoma, or a tuberculoma. The diagnosis obtained by this method is, in certain instances, helpful to the thoracic surgeon in determining definitive therapy.



Fig 336—Anteroposterior and lateral roentgenograms to demonstrate a large unilateral abscess with fluid level in the lower lobe secondary to a primary bronchogenic carcinoma of the main stem bronchus (Courtesy of Dr. C. A. Brasher, Missouri State Sanatorium, Mount Vernon, Mo.)

**Differential Diagnosis**—There are a few benign rare tumors of the bronchi which include *leiomyoma*, *neurofibroma*, *fibroma*, and *chondroma*. These tumors usually grow rather slowly, and their presenting symptoms and signs are due to variable degrees of bronchial block. They are much rarer than either bronchial adenoma or bronchogenic carcinoma, and the diagnosis is easily resolved by the microscopic examination of a bronchoscopic biopsy.

**Carcinoma of the trachea** is extremely rare. Culp could find only 147 cases in the literature. It occurs most frequently in the lower third of the trachea where squamous carcinoma most frequently develops. If the tumor occurs in the upper third, it is more often a cylindroma-like tumor of mucous and salivary

the apparently involved bronchus, and stained the slides according to the method of Papanicolaou. The tumor cells are well preserved by this method, and in a few instances unequivocal tumor cells have been found in cases in which the bronchoscopy had been negative, the roentgenographic and clinical examination only suggestive. Herbut reported on seven patients in whom cancer cells were present in bronchial secretions, although the bronchoscopic examination had been negative. Bronchoscopic aspiration therefore, has a definite though limited usefulness in the diagnosis of occult small primary peripheral tumors of the bronchi.



Fig. 22.—Bronchogenic carcinoma showing complete atelectasis of the right lower lobe with deviation of the heart to the affected side and constriction of the thoracic cage.

*Biopsy of Lymph Nodes or Skin Nodules*—The biopsy of peripheral lymph nodes particularly supraclavicular and axillary nodes is successful in making a diagnosis in about 20 per cent of the cases. When skin metastases from a primary bronchogenic carcinoma occur these areas may also be biopsied and the point of origin suspected if the patient is a male between 40 and 70 years with respiratory symptoms.

*Pleural Fluid Sediment*—At times, a definite diagnosis can be made by spinning down pleural fluid and sectioning the pellet obtained. The fluid is

*Hamartomas* of the lung are rare, McDonald has reported twenty-three cases. They can mimic peripheral bronchogenic carcinomas. They probably arise from an abnormal development of the bronchial anlage. These neoplasms occur within the parenchyma of the lung (usually subpleurally), vary in size from 0.2 cm to 9 cm, are sharply demarcated on cut section, are fairly homogeneous, and often contain bone. They are teratomas and have never been known to become malignant. Microscopically hamartomas are made up predominantly of cartilage but invariably also contain fat, smooth muscle, and glandular, often ciliated, epithelium. Roentgenologically, a well delineated sharply circumscribed mass is seen. The best treatment is surgical excision.

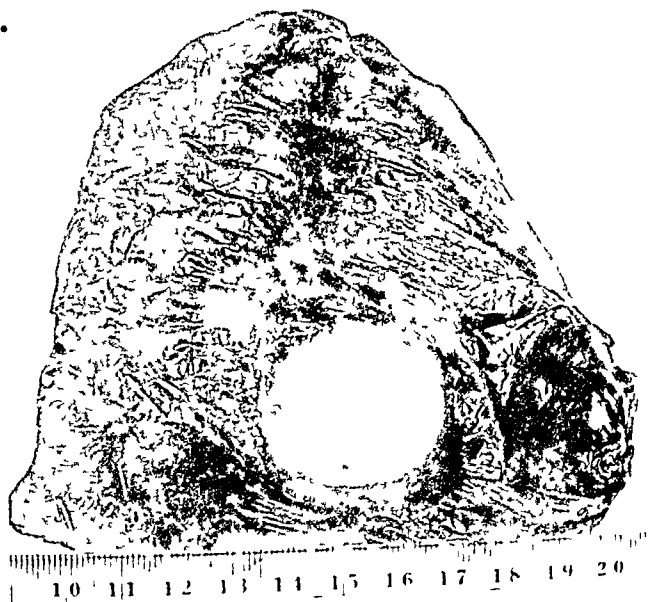


Fig. 338—Gross specimen of a well-delineated partially calcified tuberculoma of the right lower lobe. This was diagnosed by roentgenogram because of the punctate areas of calcification within it.

*Lung abscess* has to be differentiated from both bronchial adenoma and bronchogenic carcinoma, for the abscess may develop secondarily to bronchial block. If the underlying cause of an abscess is not clear, the possibility of a bronchogenic tumor should be considered and ruled out by bronchoscopy, particularly if the onset of the abscess is insidious and it occurs in an elderly male. A tuberculoma casts a solid roentgenographic shadow, but in contrast to peripheral bronchogenic carcinoma, it does not have central rarefaction (Fig. 338). Roentgenograms may show calcification in the wall of the lesion.

*Metastatic carcinoma* can rarely involve hilar lymph nodes and secondarily ulcerate through the bronchi to simulate a primary bronchogenic carcinoma. In

land type Because of the location of the tumor, respiratory symptoms due to mechanical embarrassment are prominent The tumor may act as a check valve which gradually increases to produce complete obstruction of the trachea Any treatment usually meets with failure Tracheal fissure and electrocoagulation have been advocated by Figs, but the prognosis of this group of tumors is almost uniformly poor, with the exception of the cylindroma According to Tinney, the cylindroma responds to roentgentherapy he reported three patients living five years after treatment



Fig. 337.—Roentgenogram of the chest demonstrating healed calcified foci of tuberculosis in the right upper lobe The left upper lobe shows a shadow of increased density radiating out from the hilum which was secondary to an entirely unexpected bronchogenic carcinoma of the left upper lobe bronchus The tuberculosis clouded the diagnosis (Courtesy of Dr. C. A. Brashear, Missouri State Sanatorium, Mount Vernon, Mo.)

*Tuberculosis of major bronchi* usually presents no difficulty in diagnosis, for the sputum is invariably positive for acid fast bacilli The lesions are usually multiple by bronchoscopy and there is no fixation of the mediastinum or widening of the carina

The superior pulmonary sulcus syndrome in bronchogenic carcinoma can be simulated by any other lesion located in the same area and involving the same structures such as *bronchial cyst*, *carcinoma of the thyroid*, *Hodgkin's disease*, and *metastatic carcinoma* (Herbut) The syndrome of obstruction of the superior vena cava can also be due to *lymphosarcoma*, *Hodgkin's disease*, *metastatic carcinoma* or *aortic aneurysm* (Hussey)



*Pre- and Postoperative Care*—Preoperatively the cardiorespiratory and renal status must be evaluated. Anemia should be counteracted by transfusions. Penicillin and vitamin C should be given prophylactically. A very well trained anesthetist is of utmost importance for the anesthetic agents concern cyclopropane nitrous oxide or ethylene combined with ether and oxygen given through an endotracheal tube connected with a closed system and with some arrangement for carbon dioxide absorption. Oxygen is given postoperatively.

The advances in thoracic surgery have materially decreased operative mortality. A postoperative death in the first seventy-two hours may of course be caused by an accident at the time of operation with perforation of large vessels, but far more frequently it is due to pulmonary edema. Many of these patients suddenly develop abnormalities of rhythm and heart failure. The late causes of death are due to various types of infection particularly pneumonia of the remaining lung or opening of the bronchial stump.

The number of patients with bronchogenic carcinoma suitable for operation is small. However if there are no signs contraindicating exploration, it should be done without hesitation. In 1912 Adler wrote "There should be—it is emphatically here stated—as little hesitation in resorting to an exploratory thoracotomy as there is nowadays in submitting to an exploratory laparotomy." This concept was revolutionary at that time and has only been fully accepted in recent years. At exploratory thoracotomy the tumor may be so extensive that its removal is impossible (chest wall involvement extension to parietal pleura mediastinal fixation direct involvement of pulmonary artery, vena cava or azygous vein). These findings negate further treatment after confirmatory biopsy is done.

*Bronchial adenomas* are the most common of the benign tumors of the bronchi. Although they make up only about 5 per cent of all bronchogenic tumors in Churchill's series they made up 30 per cent of the resectable group. These tumors are infrequently entirely intraluminal and in practically all instances have a large extrabronchial component. It is questionable whether bronchoscopic removal is justified because it is impossible to determine by bronchoscopy whether a tumor is entirely within the lumen. Only when the tumor has locally extended to the trachea beyond possible surgical removal or when the patient is too poor a surgical risk should removal by bronchoscopy be attempted (Chamberlain). It is logical that the treatment be surgical, for although bronchial adenomas have a long clinical evolution eventually because of pulmonary infection death results. The most debatable question is whether a lobectomy or a pneumonectomy should be done. If bronchiectasis involves other lobes of the lung besides the one in which the bronchial adenoma is primary, there is no question but that pneumonectomy is the treatment of choice. When the tumor and the secondary changes are localized to one lobe, Sweet (1945) feels that lobectomy is sufficient but Graham (1945) believes that pneumonectomy should be carried out. Pneumonectomy appears more logical because it implies a more adequate removal of possibly involved regional lymph nodes.

our experience this has been most frequently due to primary malignant tumors of the testicle. In practically all instances, however, the testicular tumors are obvious and the stage of the disease advanced. Single metastatic nodules within the lung can be very readily confused with a peripheral bronchogenic carcinoma. This will occur particularly when the primary neoplasm gives no signs or symptoms. At times aspiration biopsy is successful in making a differential diagnosis. Bilateral metastatic carcinomas forming small nodules such as from the breast, thyroid, or ovary can be confused with alveolar carcinoma. However, in most instances the primary neoplasm is clinically obvious. From the standpoint of probability if a patient demonstrates multiple nodules in both lungs the chances are far greater statistically that this is metastatic rather than a primary alveolar carcinoma.

The differential diagnosis of pleural mesothelioma is usually first concerned with *pleural effusion* due possibly to tuberculosis. The diagnosis is often resolved by the absence of tuberculosis elsewhere, plus the absence of tubercle bacilli and the presence of tumor cells in the pleural fluid. Exploratory thoracotomy with biopsy will further serve to differentiate if necessary.

### Treatment

**SURGERY**—The surgical treatment of *bronchogenic carcinoma* is pneumonectomy carried out as radically as possible for regional lymph nodes are frequently implicated. This procedure is comparatively new and it is only in the last few years that the surgical management of these patients has become clarified. The first successful pneumonectomy was performed by Graham in 1933. The lymphatic drainage is not divided by lobes, and it is therefore illogical to perform a lobectomy rather than a pneumonectomy (Ochsner). The operability of cases of bronchogenic carcinoma is not more than 15 per cent (Edwards), for the tumor is seldom diagnosed early. The operative mortality, however, has steadily decreased. Graham's last seventy cases had an operative mortality of 30 per cent and the last 25 cases, only 12 per cent. Evidence of distant metastases and extensive local disease are categorical signs which contraindicate a thoracotomy. Distant metastatic disease may appear as skin nodules, roentgenologic evidence of bone metastases (ribs, vertebrae, skull), roentgenologic evidence of disease in the opposite lung, and pathologically proved lymph node metastases (suprahilar, hilar, and axillary). Other clinical and laboratory signs give evidence of local spread beyond the possibility of surgical removal. A left recurrent laryngeal paralysis with paralysis of the left vocal cord may be present. Radioscopic examination may show a paralyzed leaf of the diaphragm due to involvement of the phrenic nerve. Bloody pleural effusion is evidence of extension to the pleural surface. Serous fluid may be due simply to changes in pressure, so that unless tumor cells are demonstrated microscopically, it is not a contraindication to surgery. The bronchoscopic examination may reveal fixation of the mediastinum with a flattened carina. Severe pain in the thoracic region or down the arm usually indicates involvement of the intercostal or brachial nerves. Practically all superior pulmonary sulcus tumors are inoperable (Graham).

In evaluating statistics on bronchogenic carcinoma it should be remembered that urban clinics, staffed with prominent thoracic surgeons, receive a disproportionate number of early pre-selected cases. As many as 50 to 60 per cent of these cases may be explored and 15 to 20 per cent resected with expectation of cure, but even from this material five-year survival rates still remain under 5 per cent of the entire group. Edwards' figures, quoted in the foregoing, reflect the over-all still gloomy outlook of carcinoma of the lung.

The prognosis of *bronchial adenoma* is usually excellent with surgical resection. Death occurs only when overwhelming infection has developed before operation. In seventeen patients reported on by Churchill, fifteen were living three to five years after surgical treatment.

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In either instance, in the hands of experienced thoracic surgeons the operative mortality is 5 per cent or less

Infrequently pleural mesotheliomas can be treated by surgical resection (Stout)

**RADIOTHERAPY**—The pathologic nature of carcinoma of the lung would make it, in principle, eligible for radiotherapy. Most of the bronchogenic carcinomas show a definite often marked radiosensitivity. In spite of this radiotherapy has little to offer in the treatment of carcinoma of the lung outside of a frequent and definite palliation (Pohle). A definite prolongation of life may also result from the judicious application of this form of treatment (Widmann). The administration of roentgentherapy quite often results in a diminution of the tumor and reestablishment of bronchial permeability, disappearance of atelectasis with disappearance of pain, improvement of the general condition and a sensation of well being. But a definite sterilization of the tumor does not follow and it is questionable whether such result is possible with our present means of roentgentherapy. The difficulty lies in the fact that even in the earliest cases, the melting of the tumor results in inflammatory complications (mediastinitis, gangrene of the lung, and formation of an abscess). In more undifferentiated tumors in spite of greater radiosensitivity, the difficulty lies in the metastatic spread and the impossibility of irradiating the entire node bearing area.

Consequently, in no case is it justifiable to treat a carcinoma of the lung by means of radiation therapy when surgery is possible. In the large group of inoperable cases, radiotherapy has a definite place and contributes definite, sometimes unexpected, results. The protracted administration of roentgen therapy offers the greatest benefit, resulting in a slow diminution of the tumor and avoiding immediate complications. High voltage roentgentherapy having the advantage of a greater penetration may possibly become of greater usefulness. Hocker reported on a group of ninety-three patients treated with 1 million volt equipment and concluded that the relative improvement of results warranted the use of higher voltage roentgentherapy.

### Prognosis

The number of resectable and therefore possibly curable cases of *bronchogenic carcinoma* is unfortunately relatively small. Of 1,016 consecutive cases reported by Edwards (1946), exploratory thoracotomy alone was done in 103 patients, pneumonectomy was done in sixty-six additional patients and lobectomy was done in four patients. Thirteen patients were living two to five years following treatment, at the time of the publication; five of these patients had lived from seven to ten years. All patients who had lobectomies died.

Certainly the more undifferentiated the tumor the worse the prognosis. It is also true that the prognosis is related to regional lymph node involvement so that more careful attention should be paid to the examination of regional node areas. If any compromise surgical procedure less radical than a pneumonectomy is done for a bronchogenic carcinoma, the prognosis is poor.

## Chapter VIII

### TUMORS OF THE THYROID GLAND

#### Anatomy

The thyroid gland lies over the trachea at the lower anterior midline of the neck. It consists of two rounded pyramidal lobes extending from the thyroid cartilage to the sixth tracheal ring and of a connecting median isthmus near the lower pole of the lobes which covers the second, third, and fourth tracheal rings. Each lateral lobe is posteriorly related to the carotid sheath and the esophagus and medially to the tracheal wall and recurrent laryngeal nerve (Fig 339). The gland is enveloped in a connective tissue capsule, and the pretracheal fascia firmly fixes it to the cricoid and thyroid cartilages.

An arterial anastomosis between the capsule and the fascial sheath is supplied to each lobe by the superior thyroid branch of the external carotid artery, an inferior thyroid branch of the thyrocervical trunk, and rarely a single small branch from the innominate artery at the midline. Three sets of venous channels are present: the superior and middle thyroid veins draining to the internal jugular and the inferior thyroid veins draining to the respective innominate veins (Fig 340).

**Lymphatics**—The lymphatics of the thyroid gland originate around the thyroid follicles and form a delicate but rich network which extends into the gland (Fig 341). The collecting trunks gather into six main groups (Rouvière):

1 *The median superior trunks* arise in the superior portion of the isthmus and adjacent areas of the lateral lobe. They travel upward in front of the larynx and then laterally to end in the subdiaphragmatic group of nodes of the internal jugular chain. In about half of the cases, some of these trunks are interrupted by an intercricothyroid lymph node.

2 *The median inferior trunks* descend along the inferior thyroid vein and usually drain into the lymph nodes of the transverse pretracheal chain. Some of these lymphatics may fail to make this first stop and continue onward to drain directly into a large lymph node at the junction of the brachiocephalic trunks. A group of lymphatics arising from the posterior surface of the lower pole of the lateral lobes, the *posteroinferior collecting trunks*, drain into the recurrent chain of lymph nodes of the same side and thus constitute a lateral continuation of the inferior median collecting trunks.

3 and 4 *The right and left lateral trunks* arise from the lateral lobes, some of them follow an upward direction and drain into the anterosuperior nodes of the internal jugular chain and others follow a transversal direction and end either in the inferior and external nodes of the internal jugular chain or in the central nodes of this same chain.

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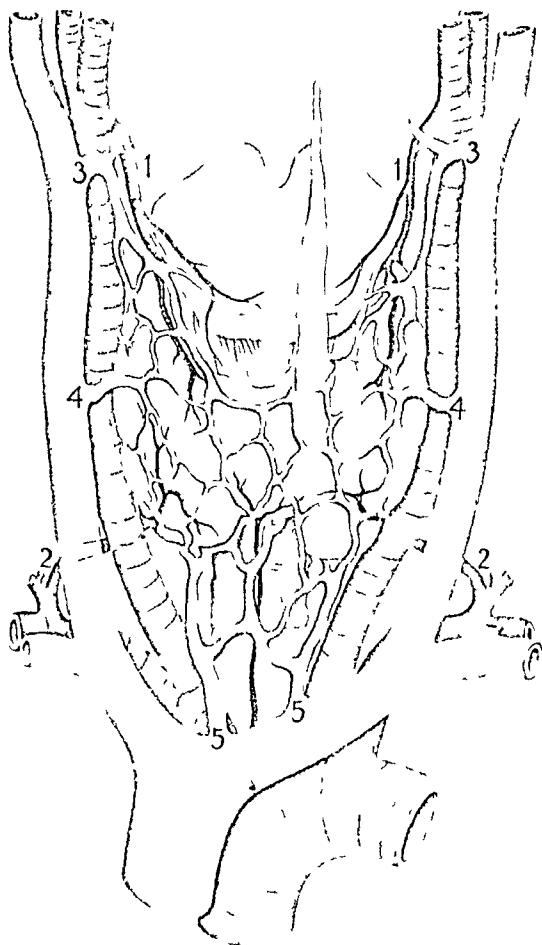


Fig. 310 —Schematic representation of the abundant vascularization of the thyroid gland. Note: 1, superior thyroid branch of the external carotid artery; 2, inferior thyroid branch of the thyrocervical trunk; 3, the superior thyroid vein and 4, the middle thyroid vein both draining into the respective jugular; and 5, the inferior thyroid veins draining into the innominate vein.

5 and 6 The *posterosuperior trunks* are present in only about one fifth of the cases. They arise from the posterosuperior region of the lateral lobes, ascend past the lateral border of the pharynx and terminate in the lateral retropharyngeal node.

In summary, the lymphatics of the thyroid gland are drained by the lymph nodes of the internal jugular chain and recurrent chain and by the pretracheal and retropharyngeal lymph nodes.

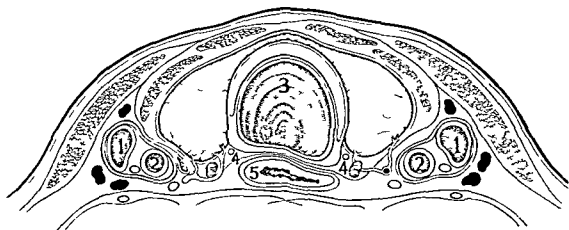


Fig. 339—Transverse section of the neck at the level of the third tracheal ring. Note the intimate relationship of the thyroid gland to 1 jugular vein, 3 carotid artery, 5 trachea, 2 recurrent laryngeal nerve and 5 esophagus.

### Incidence and Etiology

Carcinoma of the thyroid is most commonly seen in patients between the ages of 40 and 70, it is sometimes encountered between 20 and 40 years but is extremely rare under 20 years of age (Clute and Warren). The tumor predominates in the female in a ratio of about 7 to 1, and there is a difference in the age incidence for the different types of tumor (Figs. 342, 343 and 344).

About 90 per cent of all malignant neoplasms arise in pre-existing long-standing adenomas. Carcinoma of the thyroid is not related to exophthalmic goiter inasmuch as in practically every case of carcinoma there is no true elevation of the basal metabolic rate. It is interesting to note that 8 per cent of all exophthalmic goiters present coincidental fetal adenomas (Clute, 1933). If carcinoma appears in conjunction with a hyperplastic thyroid it arises not on the basis of hyperplasia but has its site of origin in a small adenoma hidden within the hyperplastic gland (Goetsch).

Berard states that in endemic goiter areas 2.5 to 4 per cent of all the malignant tumors arise from the thyroid but that in goiter-free zones the percentage is only 0.4 or 0.5 per cent. Undoubtedly a correlation may be drawn for when goiter is endemic neoplasms of the thyroid occur in significantly greater numbers.

### Pathology

**Gross and Microscopic Pathology**—The histologic classification of carcinoma of the thyroid has a practical significance in that each type has its own



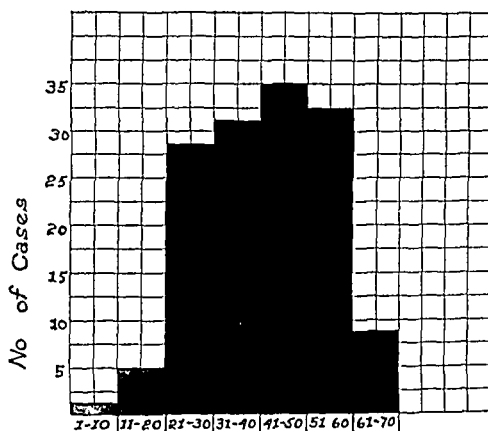


FIG. 312.—Age incidence of a group of 150 patients with potentially malignant tumors of the thyroid gland. Note high incidence in younger patients. (From Clute H. M. and Warren S. Surg. Gynec. & Obst. 1935.)

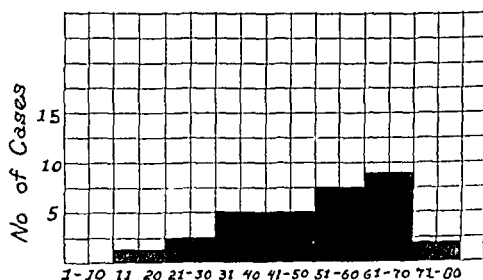


FIG. 313.—Age incidence of thirty-one patients with moderately malignant tumors of the thyroid gland. (From Clute H. M. and Warren S. Surg. Gynec. & Obst. 1935.)

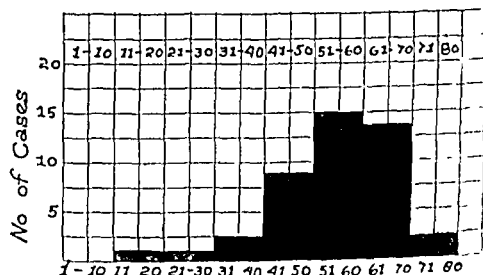


FIG. 314.—Age incidence of forty-five patients with highly malignant tumors of the thyroid gland. Note high incidence among older patients. (From Clute H. M. and Warren S. Surg. Gynec. & Obst. 1935.)

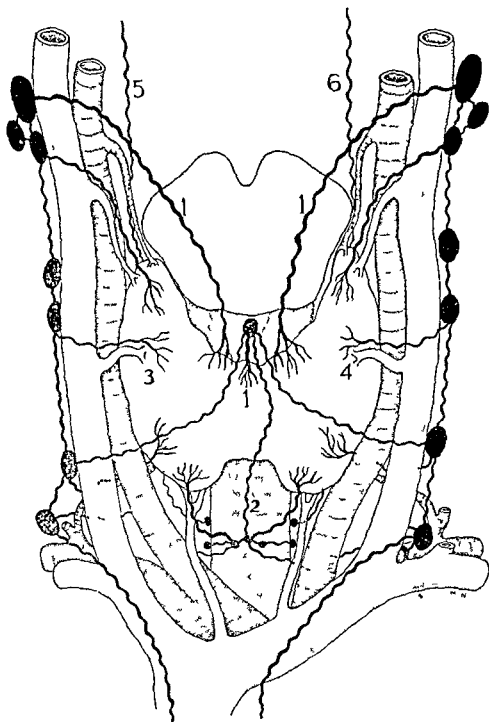


Fig 341—Schematic representation of the lymphatic trunks draining the thyroid gland. 1 The median superior trunk 2 the median inferior trunk 3 and 4 the right and left lateral trunks 5 and 6 the posterosuperior trunks. All of these are drained by the lymph nodes of the internal jugular chain and recurrent chain and by the pretracheal and retropharyngeal lymph nodes.

About 3 per cent of all adenomas show evidence of blood vessel invasion. If this invasion is shown grossly, they must be classified as definitely malignant. If invasion is present only on microscopic examination, the adenomas should be regarded as potentially malignant, although there is a 95 per cent chance that the tumor will never show any evidence of metastases.

**Papillary Cystadenoma**—The papillary cystadenoma is not seen quite so frequently as the adenoma. It usually forms papillary projections with a single layer of cells. Hemorrhages within this tumor are very common. The tumor is usually cystic with serous and frequently blood-tinged fluid. There may be difficulty in differentiating these lesions from malignant tumors, for even the most innocent-appearing papillary cystadenoma is capable of metastasizing if it has invaded a blood vessel.

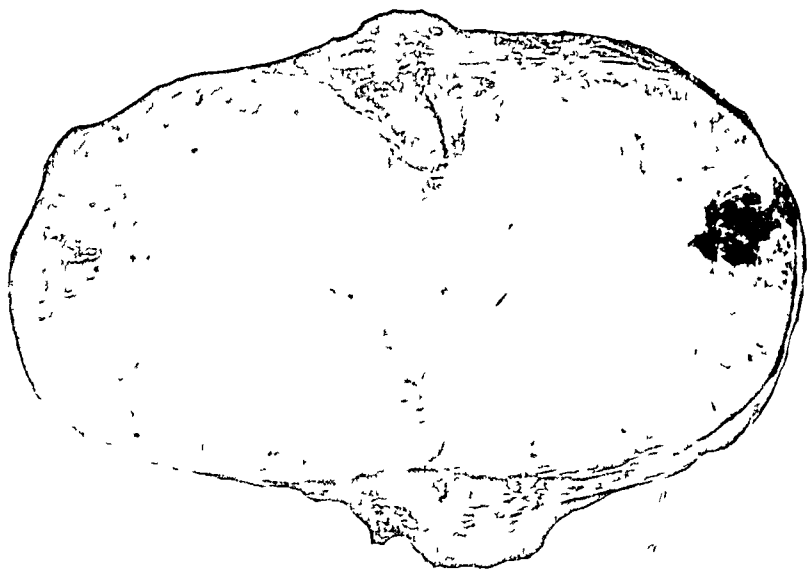


Fig. 345—Gross specimen of a benign adenoma of the thyroid. Note complete encapsulation with compression of contiguous thyroid gland and typical central fibrosis and hemorrhage.

**MALIGNANT NEOPLASMS**—The group of *potentially malignant* tumors of the thyroid is the largest and includes the adenoma and the papillary cystadenoma, classified as potentially malignant if they have gross evidence of blood vessel invasion, invasion of the capsule, or microscopic evidence of blood vessel invasion (Fig. 347). Care must be taken to prove that the blood vessel invasion is real, for it can be artifact. The adenomas most prone to have blood vessel invasion are of embryonal or fetal type. The papillary cystadenomas vary considerably in their degree of neoplastic alteration. In their most malignant form there is vastly increased stratification of the epithelium, much greater disorganization of architecture, and increased speed of growth.

prognosis The following classification of thyroid tumors by Warren (1941) is excellent and is used here as a basis for this discussion

#### Benign

- 1 Adenoma
  - a Embryonal
  - b Fetal
  - c Simple
    - 1 Hurthle cell
  - d Colloid
- 2 Papillary cystadenoma

#### Malignant

- Group I Low or Potential Malignancy
  - 1 Adenoma with blood vessel invasion
  - 2 Papillary cystadenoma with blood vessel invasion
- Group II Moderate Malignancy
  - 1 Papillary adenocarcinoma
  - 2 Alveolar adenocarcinoma
  - 3 Hurthle cell adenocarcinoma
- Group III High Malignancy
  - 1 Small cell carcinoma (carcinoma simplex)
    - a Compact type
    - b Diffuse type
  - 2 Giant cell carcinoma
  - 3 Epidermoid carcinoma
  - 4 Fibrosarcoma
  - 5 Lymphoma

#### BENIGN NEOPLASMS —

**Adenoma**—The benign adenoma is the most common of the thyroid tumors presenting a discrete well encapsulated nodule weighing from 25 to 200 grams. It probably arises from the epithelium of pre-existing follicles rather than from rests of embryonal epithelium. It has a definite complete connective tissue capsule which becomes more fibrotic as the lesion grows and which shells out easily. It compresses the adjacent thyroid tissue (Fig. 345). The benign adenoma should be differentiated from the nodules so frequently found in the adenomatous goiter which do not have a complete connective tissue capsule. Gross evidence of blood vessel invasion should be searched for.

The microscopic appearance of the benign adenoma shows many variants (Fig. 346). The two most common types (embryonal and fetal) are formed by embryonal cells or small follicles. The rare so-called Hurthle cell adenoma is made up of large cells with acidophilic granular cytoplasm. The simple colloid adenoma is formed by follicles distended with colloid material. It should be emphasized that the microscopic appearance of the benign adenoma may suggest a malignant lesion, but if encapsulation is present and there is no evidence of blood vessel invasion either grossly or microscopically the tumor must be classified as benign. By contrast it may appear benign because of its regular pattern but if blood vessel invasion and invasion of capsule are present it is malignant.

The papillary cystadenocarcinoma arising from so-called aberrant thyroid has been long a debated entity. It is now generally admitted that practically all of these tumors represent metastases from small nonpalpable primary papillary cystadenocarcinomas in the thyroid gland (King 1942). If aberrant thyroids arise from the lateral anlage of the thyroid then tumors should lie between the carotid sheath and the thyroid lobe laterally and the esophagus and trachea medially (Weller). Almost all so-called lateral aberrant thyroid tumors however lie superficial or external to the carotid sheath. King further points out that although many thousands of radical neck dissections have been performed for conditions other than cancer of the thyroid no aberrant thyroid has ever been found. This further substantiates the concept that *so-called lateral aberrant thyroid tumors are in practically all instances metastatic implants rather than primary tumors*. In fifty-one supposedly lateral aberrant thyroid tumors in which the thyroid itself was examined, the primary source was found in the thyroid in thirty-one cases and in nineteen of these the primary lesion and the cervical metastases were both on the same side.

King's Pathologic study further substantiated the evidence that the thyroid tumor was primary and that the neck nodules were lymph node metastases. In most instances the cervical masses were multiple, well delineated, not attached to the skin and located along the jugular chain of lymph nodes, in other words they had all the characteristics of metastatic nodes. In 55 per cent of these supposedly aberrant thyroid tumors lymphoid tissue was present and even peripheral sinuses containing tumor cells were observed. It is interesting to add that in only one of the primary thyroid lesions did lymphoid tissue seem to be part of the neoplastic process.

The group of *moderately malignant* tumors of the thyroid is composed of the papillary adenocarcinomas which are papillary structures with stratification of the cells, the alveolar adenocarcinomas which form small but rather uniform acini (Fig 348) and the rarest type the Hürthle-cell adenocarcinoma in which individual cells resemble those observed in the Hürthle-cell adenoma but in which signs of malignant change are present (Fig 349).

The highly malignant group of tumors, which fortunately makes up only a small percentage of all thyroid tumors, is the small-cell carcinoma whose cells are quite uniformly small with innumerable mitotic figures (Fig 350). This type of tumor may develop suddenly in a nonadenomatous gland. The very undifferentiated carcinoma in which giant cells are common (Fig 351) progresses with great rapidity and quickly replaces the gland which may become rather large. The epidermoid carcinoma is an extremely rare tumor and probably arises from remnants of the thyroglossal duct.

Tumors of a high degree of malignancy show a greater and more rapid local invasion. The local spread of a carcinoma of the thyroid may involve the recurrent laryngeal and vagus nerves, the subcutaneous tissues and muscle. The only muscle in the thyroid area which escapes complete destruction is the sternocleidomastoid. Tumor may surround or invade the trachea down to the submucosa causing edema and sometimes ulceration but its cartilaginous rings and fibrous sheaths make the trachea somewhat resistant to involvement.



Fig 346—Photomicrograph of a benign adenoma of the thyroid gland. Note complete encapsulation, central degeneration, and striking difference between histology of adenoma and contiguous compressed thyroid gland (low power enlargement).



Fig 347—Photomicrograph of a potentially malignant papillary cystadenoma of the thyroid gland showing blood vessel invasion (low power enlargement).

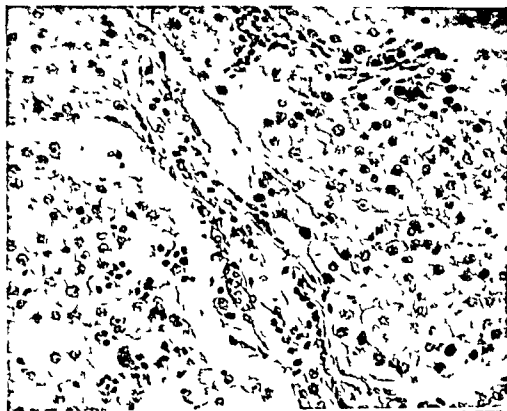


Fig. 349

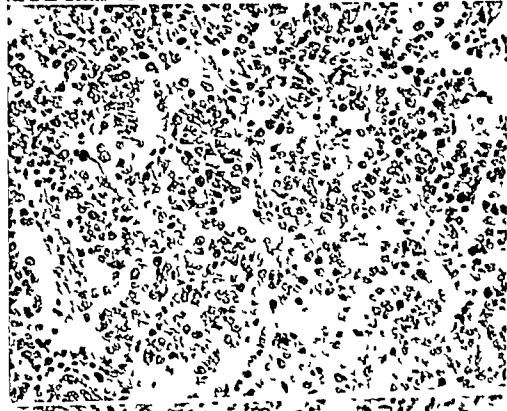


Fig. 350

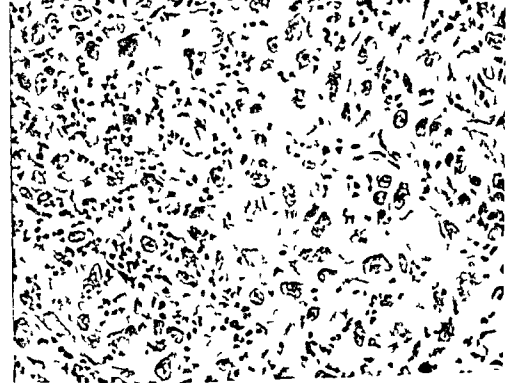


Fig. 351

Fig. 349—Photomicrograph of a fourth-cell adenocarcinoma (high power enlargement). This tumor belongs in the category of moderately malignant tumors. (Slide contributed by Dr. Shields Warren, New England Deaconess Hospital, Boston, Mass.)

Fig. 350—Photomicrograph of a small-cell carcinoma (high-power enlargement). This tumor belongs in the highly malignant group of tumors of the thyroid gland. (Slide contributed by Dr. Shields Warren, New England Deaconess Hospital, Boston, Mass.)

Fig. 351—Photomicrograph of a giant-cell carcinoma of the thyroid gland (high power enlargement). This tumor belongs in the highly malignant group. (Slide contributed by Dr. Shields Warren, New England Deaconess Hospital, Boston, Mass.)

It may also invade and even ulcerate the esophagus. Spread to neighboring bones particularly the clavicle and sternum, is not unusual.

The fibrosarcoma and the lymphosarcoma are only questionably primary tumors of the thyroid, in most instances probably representing undifferentiated carcinomas. If enough sections are cut of the tumor resembling a fibrosarcoma areas of glandular formation are invariably found. It is within the realm of possibility that a fibrosarcoma can arise from the existing stroma but there are only a few of these cases in the literature which seem authentic (Zeckwer). The demonstration of fibroglia fibrils is very strong confirmatory evidence. Microscopically lymphosarcomas may be quite closely simulated but the distribution of the metastases, the normal basal metabolic rate and the failure to respond rapidly to radiation therapy make it very likely that most of the tumors classified as lymphosarcoma are really carcinomas.



Fig 348—Photomicrograph of a malignant alveolar carcinoma (low power enlargement)

**METASTATIC SPREAD**—The regional metastasis of the adenoma and the papillary cystadenocarcinoma by blood vessel invasion and of the papillary cyst adenoma with regional metastases (Group II) may be very slow. It is not at all unusual for these tumors to recur after several years or for metastases to remain in the cervical and mediastinal nodes or the lungs for as long as five years. Regional lymph node metastases are almost invariably present unilateral when the tumor is unilateral. But if the thyroid is totally invaded then the adenopathy is bilateral. The nodes along the larynx trachea and the external jugular vein are commonly invaded and, later, the submaxillary, supraclavicular, mediastinal, and retrosternal nodes may become involved. Posteromedial lymph node involvement is rare.

The organs most frequently affected by metastatic disease are lymph nodes lungs bone liver kidneys and brain. Pulmonary metastases are usually mul-



than malignant change. The adenoma which becomes malignant or the papillary cystadenoma which grows rather slowly usually metastasize to the regional lymph nodes. These nodal masses may be the only sign of disease because the primary tumor in the thyroid may be very small and not palpable.

It is interesting that in more than one-half of the patients with carcinoma of the thyroid there is a history of enlargement of the organ for five years or longer. Very few tumors are diagnosed before one year has elapsed (Wilson). Dysphagia usually accompanies malignant neoplasms of the thyroid. As the tumor begins to cause pressure on the larynx, voice changes may appear. With further increase in size, recurrent laryngeal paralysis takes place, and, still later, there may be pronounced respiratory difficulty due to edema and compression of the trachea. Invasion of the trachea may result in hemoptysis. If the tumor grows around the veins of the neck, there may be evidence of obstruction in the superior vena cava accompanied by choking attacks and a sensation of fullness in the neck.

Potentially malignant and moderately malignant tumors usually present a distinct symmetrical nodularity of the thyroid, sometimes with fixation. In highly malignant tumors often there is no history of a previous adenoma. The mass appears within the thyroid, grows very rapidly, and symptoms due to pressure appear early. Surgical removal is rapidly followed by local recurrence and death may ensue within a year after onset.

A small number of carcinomas of the thyroid have symptoms from bone metastases as the first clinical manifestation of disease, the primary tumor being very small or nonpalpable. These metastatic growths may pulsate, and, when they occur in the femur or humerus they often cause fractures.

Rarely, the metastatic thyroid tissue may show function. Von Eiselsberg reported a case in which a total thyroidectomy had been performed by Billroth. This operation was followed by myxedema, but after sternal metastases appeared the myxedema disappeared. Milles reported a case in which extract from metastatic lesions of the lung and bone injected into tadpoles produced accelerated growth and maturation.

### Diagnosis

The best method of palpating a case of suspected *adenoma* is for the physician to stand behind the patient, whose head is in hyperextension, and place the fingers just above the thyroid. When the patient swallows, the tumor will be felt to rise and slip back abruptly. These tumors are unilateral, asymmetrical, sharply delineated, and not fixed to the overlying skin. If there has been displacement of the trachea without resultant respiratory difficulty, the tumor is probably benign rather than malignant. When the adenoma becomes malignant it then presents as a localized fixed firm tumor. In the small group of highly malignant carcinomas, the tumefaction may be diffuse and hard and may fix all surrounding structures to it. The cervical lymph nodes should always be examined for evidence of metastases. Bone metastases may present areas of localized tenderness, and a soft tissue pulsating

multiple and often subpleural. There is a striking tendency for thyroid tumors to metastasize to bone. In 110 cases collected by Bernard and Dunet, the bones of the skull were involved in 25.6 per cent, the vertebral column in 21 per cent, the humerus, femur, sternum, ribs, and pelvic bones in from 7 to 10 per cent each, and the clavicle in 4 per cent. These metastases usually appear in the spongy portion of the bone, are richly vascularized, and may pulsate. Tumor appears between the compact tissue of the flat bone of the skull, in the bodies of the vertebrae, in the manubrium, in the epiphysis or in the medullary cavity of the long bones. Spontaneous fractures can occur.

### Clinical Evolution

*Adenomas of the thyroid often remain latent for a considerable period of time. They may be discovered accidentally by the patient or during a routine physical examination. As they increase in size however, pressure symptoms due to distortion of the larynx or to compression of the trachea may occur.*



Fig. 30.—Adenocarcinoma of the thyroid gland.

A high percentage of thyroid carcinomas are preceded by adenomas. If an adenoma becomes malignant, it becomes firm and fixed, and symptoms may be caused by local invasion of neighboring structures. A sudden rapid increase in the size of an adenoma usually means hemorrhage within it rather

*Metastatic lesions in the thyroid* from primary tumors elsewhere are unusual but may occur from carcinomas of the breast, lung, or kidney or from melanocarcinomas. If a metastasis is present in the thyroid, it is usually only part of a generalized process (Mayo). Hodgkin's disease may rarely involve the thyroid. Carcinoma of the oral cavity practically never metastasizes to it. Other tumors of the thyroid gland such as plasmocytoma (Shaw), osteogenic sarcoma (Brudeis), and teratomas (Potter) are of extreme rarity.

### Treatment

**SURGERY**—An adenoma of the thyroid is a potentially dangerous lesion which must be surgically removed. If, on pathologic examination, it presents no evidence of blood vessel invasion, then it can be classified as benign, and no further treatment is indicated.

If, at the time of operation, there is evidence of capsular invasion by the tumor, then the tumor should be removed with the entire lobe and isthmus of the thyroid. If the entire gland is involved, radical surgery should be done, provided the tumor does not extend below the clavicle. Fixation of tumor to the trachea or esophagus is not necessarily a contraindication to surgery for it may be caused by a purely inflammatory process rather than by neoplastic invasion of those organs. Emphatically, if the tumor extends beyond the capsule, the largest possible portion of the jugular vein should be removed because of the high incidence of vein invasion in these cases. If tumor is present in one lobe of the thyroid and in the homolateral lymph nodes, then radical removal of this lobe, the isthmus, and a block dissection of the regional lymph nodes should be done. If the tumor is apparently present in the regional lymph nodes of one side only and the thyroid is normal to palpation, a homolateral hemithyroidectomy should be carried out, for in practically every instance the specimen contains the primary tumor. If, at the time of exploration, the sternocleidomastoid muscle is involved, it should also be removed. At times resection of a single bone metastasis may result in control of the disease (Morton, Crile).

The risks of surgery are negligible for the benign adenomas and the well delimited carcinomas of the thyroid. Even when a simultaneous neck dissection is indicated, the operative mortality is usually low. For highly malignant tumors, very radical surgery is necessary in spite of the higher operative risk. Mediastinal emphysema (Barric), hemorrhage, injury to the recurrent laryngeal nerve, local infections, and pulmonary complications can occur. If there is any evidence of tracheal obstruction, a tracheotomy should be done (Laher).

**ROENTGENTHERAPY**—Radiotherapy is not indicated for adenomas. There is also no evidence that postoperative roentgentherapy serves to prevent the development of recurrences. But if the tumor has metastasized to the regional lymph nodes in either potentially malignant or moderately malignant tumors, postoperative roentgentherapy undoubtedly will palliate and considerably prolong the life of the patient. If a recurrence appears from moderately malignant tumors and has extended beyond the possibility of surgical removal, then radiotherapy is of great value in reducing the size of the lesion,

mass overlying the involved bone is not unusual. Aspiration or incisional biopsy of such masses is invariably diagnostic.

The clinical diagnosis of carcinoma of the thyroid is made in less than half of all the cases. It is too often only made microscopically after the thyroid has been removed for a supposedly benign lesion. Unfortunately, the younger the patient, the less likely is the correct diagnosis made, for it is seldom even considered. At operation, if the cleavage planes are lost, if the sternothyroid muscle is densely adherent to the thyroid, and if the contour of the thyroid is no longer present, carcinoma of the thyroid should be suspected. Tracer doses of radioactive iodine tend to go to areas of metastases and may be revealed with the Geiger counter (Frantz 1944).

**Roentgenologic Examination**—Every patient with questionable carcinoma of the thyroid should have roentgenologic examination of the chest and bones to show possible pulmonary metastases and involvement of bones in the immediate neighborhood of the tumor. Bone lesions are osteolytic and present considerable destruction at times with expansion and thinning of the cortex and even fractures. The skull, vertebral column, humerus and sternum are commonly involved.

**Differential Diagnosis**—*Thyroiditis* may be confused with cancer of the thyroid. The gland is usually symmetrically enlarged and fixed to the trachea and, because of this, is immobile. Thyroiditis is often preceded by a respiratory infection, the thyroid may be somewhat tender, and the basal metabolic rate may be a bit elevated. If the thyroiditis is advanced and of the *Riedel's struma* type the gland becomes very hard and ligneous (McSwain), partial myxedema may occur with some elevation of blood cholesterol and some lowering of the basal metabolic rate. In *Hashimoto's disease* (struma lymphomatosa) the gland is quite firm but not as hard as in Riedel's struma, and the thyroid may or may not be fixed.

The presence of *metastatic cervical lymph nodes* may cause diagnostic confusion particularly if there is no palpable tumor in the thyroid region. These nodes are often thought to be tuberculosis or branchiogenic cysts, but aspiration biopsy or surgical removal will insure the correct diagnosis. When there is a tumor of the thyroid and a nodule in the neck, carcinoma of the thyroid with metastases to the regional cervical lymph nodes should be considered rather than two separate processes.

*Pulsating metastatic lesions* from carcinoma of the thyroid are often diagnosed as primary osteogenic sarcomas. If the mass is accessible, aspiration biopsy will solve the diagnosis. Usually these metastases are osteolytic. Pulsating tumors of the sternum (if they are not aortic aneurysms) are most often metastatic carcinomas from either the kidney or thyroid. In eighteen pulsating metastatic neoplasms reported by Crile nine originated in the kidney and nine came from the thyroid. Lateral view roentgenograms usually serve to differentiate an aneurysm from a metastatic carcinoma.

*Carcinoma of the parathyroid* is extremely rare but when it does occur it produces fibrocystic disease of the bone which may regress at removal of the primary tumor and then recur with metastases (Meyer).

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slowing down its progress and prolonging life. At times, when the carcinoma is far advanced and obviously inoperable, partial removal may relieve obstruction and irradiation may relieve pressure on the trachea.

Radiotherapy for bone metastases particularly from the differentiated tumors often gives striking symptomatic relief. It has been shown by Frantz (1944) that injection of radioactive iodine gives temporary respite, but this therapy is not of great practical value. Haagensen correlated the value of radiation therapy with the various histologic types of tumors of the thyroid.

### Prognosis

Of ninety nine patients with *adenoma with blood vessel invasion* reported on by Clute (1935), all were well except for three who died and for one living with a recurrence. Follow up on all these patients had been continued for at least three years. It should be pointed out that only those patients who showed evidence of blood vessel invasion developed metastatic disease. This very important point was emphasized by Graham.

The *papillary cystadenoma* used to be considered entirely benign, but undoubtedly this was because of short follow up. They have however, a good prognosis. Of fifty one patients operated on thirty six (70 per cent) were living and well at the end of three years (Clute 1935).

The *carcinomas of moderate malignancy* have a fair prognosis but the longer they are followed the more instances of recurrence and metastases appear. In Clute's (1935) series of thirty one patients, ten were living three years or longer. Frantz pointed out in the papillary adenocarcinomas that metastases may be present for long periods of time (sometimes over five years) before death supervenes. One of her patients had evidence of persistent disease for eleven years.

The *highly malignant* group of tumors no matter how radical the treatment have an almost hopeless outlook. Of forty five cases collected by Clute (1935) only six of the patients were living three years or longer. These patients often die with local invasion alone before metastases develop.

Patients with small occult carcinomas which are found incidentally have a good prognosis for they often have not metastasized at the time of operation. About 50 per cent of the patients with carcinoma of the thyroid have fairly far advanced disease when first seen and the prognosis on the whole is very poor (Clute).

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however, is the more accurate name, for multiple sections usually show the presence of tissues arising from all three layers (Harrington). They vary in size and are well-delineated structures. On section they are cystic and may contain cloudy fluid and grumous material similar to that seen in teratomas of the ovary. Calcification of the wall may be present. In a review of 233 cases of teratoid tumors, all but three were found in the anterior mediastinum (Blades, 1941). They are usually located in front of the pericardium and great vessels. Teratomas have a well-defined wall which may be lined by squamous or columnar epithelium. They contain hair, sebaceous material, and, frequently, bone, cartilage, and teeth. Numerous other organic structures such as muscle, lipoid, nerve, pancreatic tissue, intestinal tissue, salivary gland, sweat glands, and mucous glands may be present. Most of these tumors are benign, but a few become malignant. Laipply found that of 245 reported teratoid tumors, twenty eight (11 per cent) were malignant. These are usually epidermoid carcinomas, but malignant tumors can arise from any of the structures found within a teratoma. By pressure, teratomas can erode through the pleura or into the bronchi. At times, because of communication with bronchi, infection results. The epidermoid carcinomas metastasize to regional lymph nodes, lung, and other distant organs.

The most common tumor of the *posterior mediastinum* is of nerve origin. These tumors most often arise from intercostal nerves, intervertebral foramina, or from sympathetic ganglions. They vary considerably in size, are usually firm and grayish-white, tend to be encapsulated, and may have cystic areas. These tumors grow slowly and cause local destruction of contiguous structures. If they arise from nerve elements near the intervertebral foramina, they may assume a dumbbell shape, when they arise from an intercostal nerve, erosion of the inferior margin of the rib may occur. In 105 cases collected from the literature by Kent, 37 per cent were interpreted as being malignant. Microscopically they may appear as a typical neurofibroma, ganglioneuroma, or other variant of neurogenous origin. The neurofibromas may become malignant, but the neurilemmoma does not (Stout). When these neural tumors are malignant, they may locally invade neighboring structures, destroy vertebrae and ribs, and metastasize to the lung.

Tumors of the *thymus*, the third most common tumor of the mediastinum, originate either from the lymphoid tissue or from the epithelial reticulum. The carcinomas are usually quite firm, often encapsulated, and lobulated. Primary lymphosarcomas grow rather rapidly to a large bulky size, metastasize to the regional lymph nodes, and later present widespread dissemination. The epithelial carcinomas are made up of sheaths of cells, and at times bodies caricaturing Hassall's corpuscles may be present. Not too infrequently a thymic carcinoma may be composed of an intermixture of epithelial and lymphoid cells which are of the lymphoepithelioma type (Matras). The malignant neoplasms locally invade behind the sternum, implicating the pericardium, pleura, and even heart muscle (Hellwig) and metastasizing late to lungs and other organs.

## Chapter IX

### TUMORS OF THE MEDIASTINUM

#### Anatomy

The mediastinum extends as a septum between the two pleural cavities. Its walls are composed laterally of parietal pleura, anteriorly of the sternum with attached musculature, posteriorly of thoracic vertebral bodies, inferiorly of diaphragm, and superiorly of the thoracic inlet at the level of the first thoracic vertebra at the manubrium. The mediastinum is arbitrarily divided into anterior and posterior portions by the heart, surrounding pericardium, and the great vessels. Included in these dividing structures are the phrenic nerves and accompanying arteries. The anterior mediastinum contains the thymus branches of the internal mammaries, anterior mediastinal lymph nodes, and fibroareolar tissue. The posterior mediastinum includes the trachea and its bifurcation, behind which extends the esophagus with the vagi nerve plexus covering it in the inferior portion. Superiorly the vagi are lateral to these two structures. Posterior to the esophagus is the descending portion of the thoracic aorta to the left and the azygous vein to the right, between which lies the thoracic duct in the lower part of the mediastinum. Above the fifth thoracic vertebra, the thoracic duct crosses to the left and ascends to the cervical region. Closely adherent to the vertebral bodies in the most posterior portion are the right thoracic and intercostal arteries and the hemiazygous system of veins. The greater splanchnic nerves frequently enter the mediastinal compartment on the anterior aspects of the lower thoracic vertebra.

#### Incidence

Primary tumors of the mediastinum are relatively rare. Heuer collected fifty five, of which thirty eight were benign and seventeen malignant, or approximately two benign for each malignant tumor. Crosby collected thirty five cases of thymic carcinoma twenty five in males and ten in females. Carcinoma of the thymus usually occurs in patients between 50 and 70 years of age while lymphosarcomas of the thymus occur most commonly in males under 40 years or in children (Crosby). Teratomas of the anterior mediastinum usually do not become clinically manifest in patients under 30 years of age. Neurogenic tumors arising from the posterior mediastinum occur at any age and are about equally divided between sexes. Primary tumors of the heart are usually first diagnosed at post mortem examination. Only about 200 cases have been reported and they have occurred at all ages.

#### Pathology

**Gross and Microscopic Pathology**—The most common tumor of the *anterior mediastinum* is the teratoma, often designated as a dermoid cyst. Teratoma



bloody pericardial effusion. Later in the evolution they may metastasize to the axillary and regional lymph nodes.

Other primary tumors arising within the mediastinum make up a very small percentage of the group. Thymomas are often large, may be intrathoracic or extrathoracic, may be extensive, may extend up into the neck, or can be extensive in the chest cavity. Healy and McCorkle found only thirty-four cases of thymoma in their series.

### Chronic Evolution

The chronic evolution of the tumor is characterized by its early symptoms, which are usually nonspecific. The tumor may be a primary or a secondary growth. The primary growth is usually a large, well-circumscribed, encapsulated mass, which may be found in the mediastinum, the lungs, or the pleura. The secondary growth is usually a small, well-circumscribed, encapsulated mass, which may be found in the mediastinum, the lungs, or the pleura. The tumor may be a primary or a secondary growth. The primary growth is usually a large, well-circumscribed, encapsulated mass, which may be found in the mediastinum, the lungs, or the pleura. The secondary growth is usually a small, well-circumscribed, encapsulated mass, which may be found in the mediastinum, the lungs, or the pleura.

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The *benign neoplasms of the heart* include fibromas, fibromyomas, rhabdomyomas, and, less commonly, lipomas, angiomas, and teratomas. These tumors are seldom found on the valves. The myxoma, a true neoplasm, is the most common benign tumor, usually occurring in the left auricle (Fig. 353). It arises from the endocardium, may vary considerably in size, and its surface is smooth and glistening. Microscopically, cells containing mucin, inflammatory cells and abundant blood vessels are present. The other benign tumors do not vary in their gross and microscopic appearance from their counterpart elsewhere. Rhabdomyomas are often associated with tuberous sclerosis of the brain. Adenoma sebaceum of the skin, and mixed tumors of the kidney. It is questionable whether these are true tumors (Farber).



Fig. 353—Typical well-limbed myxoma arising from the left auricle. Because of the location it was erroneously thought that the patient had rheumatic heart disease. (From Decker: *Arch. Path.*, 1941.)

Primary malignant neoplasms of the heart are much less frequent than benign tumors. In 143 primary heart neoplasms collected by Mandelstamm there were 117 benign and 26 malignant. In contrast to the benign tumors the malignant tumors and particularly the sarcomas arise most frequently from the right auricle, the interventricular septum or the pericardium. A fibromyxosarcoma has been reported arising from the pulmonary artery (Haythorn). The malignant tumors can not only block the valvular orifices but can also invade the myocardium and extend into the pericardium to cause

calcification in its wall (Fig 354) or may contain teeth. The neurofibroma is located in the posterior mediastinum and is usually a well-delineated, spherical, nonpulsating shadow (Fig 355). Lobulation may indicate malignant change (Kent). Neurofibromas often show bone erosion of the ribs or spine. Primary tumors of the thymus often maintain the shape of the thymus and are best seen in the frontal projection (Hampton), lymphosarcomas often form massive, lobulated tumor masses, usually in the superior and anterior mediastinum. The lateral roentgenograms may not reveal the thymus, for

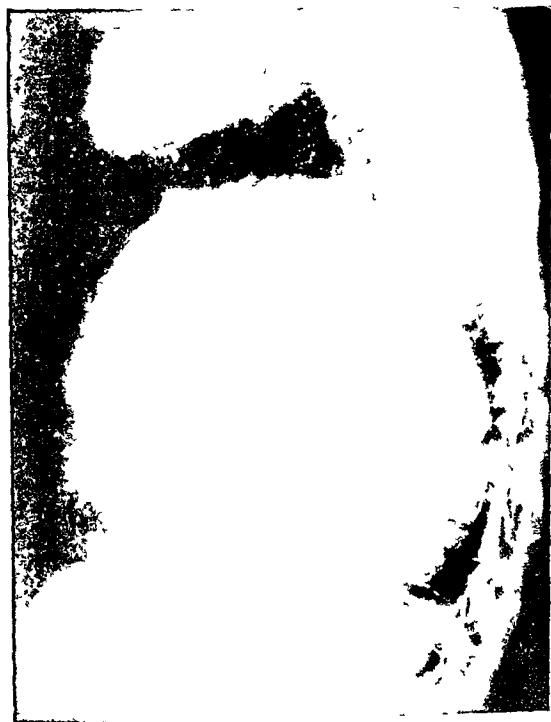


Fig 354—Lateral roentgenogram of a huge mediastinal teratoma which had been present for many years in a man 60 years of age. The tumor is well delineated with a partially calcified wall.

since it is flat and thin, its shadow is difficult to discern (Blades). A lipoma of the anterior mediastinum is often large, and the shadow is less opaque toward the periphery (Andrus). Artificial pneumothorax and particularly lipiodol may be useful in determining whether a lesion is intra- or extra-pulmonary.

The roentgenologic examination of a myxoma of the heart may reveal an enlarged left auricle, and in the malignant tumor of the heart, enlargement of

course may resemble a subacute bacterial endocarditis. The patients usually die of cardiac failure, but in a few instances death may be sudden because of occlusion of either the tricuspid or mitral orifice by a pedunculated tumor (Yater).

### Diagnosis

The diagnosis of a mediastinal tumor is usually made by roentgenographic examination. However, when clinical signs of mediastinal block appear (obstruction of the superior vena cava, Horner's syndrome, collateral circulation, dyspnea), the possibility of a mediastinal tumor should be considered. The presence of a Horner's syndrome usually indicates a lesion of the posterior mediastinum involving the paravertebral sympathetic chain (Heuer). If associated with the mediastinal tumor there is a great deal of pain, anemia, weight loss and signs and symptoms suggesting distant metastases, there is a good chance that the tumor is malignant. If the patient expectorates hair and grumous material, a definite diagnosis of a teratomatous tumor with rupture into a bronchus can be made. Occasionally a silent mediastinal tumor is discovered on routine roentgenographic examination of the chest. If the symptoms of a mediastinal tumor have been present longer than a year, the chances are high that it is benign (Haagensen).

A primary tumor of the heart seldom causes symptoms other than those due to cardiac abnormality such as cardiac failure or abnormal rhythms. Murmurs are extremely variable. Sudden attacks of extreme dyspnea or paroxysms of cyanosis may follow changes in position. Signs of a tricuspid valvular lesion with right auricular enlargement or pulmonary stenosis may suggest the presence of a primary tumor of the heart because tricuspid stenosis is very rare and pulmonary stenosis is usually congenital (Yater). If there is no obvious cause for cardiac failure, primary neoplasm of the heart may be considered but rarely has this diagnosis been made. Shelburne (1935) diagnosed a case of fibrosarcoma of the pericardium on the basis of bloody pericardial exudate and electrocardiographic evidence of bundle branch block.

The benign tumor of the mediastinum is about twice as common as the malignant tumor. If a tumor presents a well delineated homogeneous non-pulsating roentgenologic shadow and the symptoms are only those of mediastinal compression, it is probably benign. If the primary mediastinal tumor is malignant, the shadow is usually not distinct, there may be roentgenologic evidence of distant metastases, the systemic symptoms are usually more pronounced, and pain due to local invasion of surrounding structures is nearly always present. Indistinct shadows surrounding a mediastinal tumor may also represent effects due to compression or secondary infection.

**Roentgenologic Examination**—The roentgenologic examination is the most important diagnostic procedure in primary tumors of the mediastinum. Views in several planes are necessary, the lateral projection being most important. Tomography may be useful. These tumors have certain roentgenologic characteristics which may be diagnostic. The teratoma is invariably located in the anterior mediastinum and is most clearly delineated by lateral films. It usually presents a well defined outline with a definite capsule and may show

**Biopsy**—Tumors of the mediastinum very rarely ulcerate through the skin except occasionally in carcinomas of the thymus. Therefore, a biopsy entails either an exploratory thoracotomy or aspiration. An aspiration biopsy of a mediastinal tumor may be diagnostic; a neurofibroma may be recognized by its characteristic microscopic pattern, and teratomas may show gumous material and at times hair. Some of the more uncommon malignant tumors are impossible to differentiate unless incisional biopsy is done.

**Differential Diagnosis**—Mediastinal tumors must first be differentiated from non-neoplastic masses within the mediastinum. *Retrosternal goiter* is usually identified by its location and obvious association with the thyroid gland. *Aortic aneurysm* is more difficult to differentiate; this diagnosis is usually made on the basis of profile roentgenograms, positive serology, and the appreciation of pulsation. Roentgenkymography may be valuable in making a differential diagnosis (Scott), but in some cases this test alone is of no help (Fabrieus). In very few instances, the diagnosis is troublesome, for there may be a laminated clot within the aneurysm which prevents pulsation, and conversely if the tumor is attached to the aorta, then rhythmic pulsation may occur. *Tuberculomas of the posterior mediastinum* can form well delineated masses, but they may contain punctate calcification. Other infrequent lesions such as *mediastinal abscess*, *encapsulated mediastinal fluid*, and *hydatid cysts*, can all cause difficulty in diagnosis. *Tuberculosis of the vertebrae* with a paravertebral mass may be misleading if only conventional roentgenograms are taken. Lateral views show characteristic changes in the vertebrae.

Blades reported twenty-three cases of *branchiogenic cysts*. These cysts may lie along the tracheobronchial tree, but if the tumor is in the mediastinum, the most common location is in the superior mediastinum near the tracheal bifurcation. They promote pain and cough. Blades believes that the lateral roentgenogram is of the greatest diagnostic significance because the mass is indistinct in contrast to well-delineated teratoid tumors and, unlike neurogenic tumors, is not in the extreme posterior position. Brown and Robbins demonstrated that because these cysts are attached to the trachea, the mass moves with the movements of deglutition.

Because of the rarity of primary tumors of the heart, either benign or malignant, other more common conditions such as *heart failure* and mediastinal tumors are thought responsible for their symptoms. A diagnosis of a *valvular lesion* may be made because of the murmur present (mitral stenosis, tricuspid stenosis, aortic insufficiency). If auricular fibrillation or flutter or heart block is present it is often thought to be due to usual etiologic agents. In some instances angina pectoris may be present.

*Metastatic tumors* are more frequent than primary tumors of the mediastinum. The most common lesions are *lymphosarcoma* and *Hodgkin's disease*. These can be differentiated if a peripheral lymphadenopathy can be biopsied and diagnosed. In addition, these tumors show notable radiosensitivity. In most other instances, however, exploratory thoracotomy with biopsy is the surest procedure. In Heuer's group, the second most common lesion was *metastatic carcinoma* arising from near-by organs; thirty-one were metastatic from the bronchus and twelve from other organs. Carcinoma of the esophagus and



Fig. 355.—Posteroanterior and lateral roentgenograms of the chest revealing a well delineated tumor in the thorax. The lateral view shows the tumor to be located in the characteristic posterior position of a neurofibroma. (Strom Kent, E. M. J. Thoracic Surg. 1944)

Exploratory thoracotomy in the hands of a competent thoracic surgeon can be done with practically no operative risk. Blades reported 109 cases of mediastinal tumors, ninety-four benign and fifteen malignant, removed by various thoracic surgeons without a single death. The usual surgical approach for all mediastinal tumors is posterolateral. Radiotherapy is indicated in primary lymphosarcomas, but unfortunately the palliation is only transient. Radiations are reputed to have little or no effect on thymic carcinoma.

In view of the advances made in surgery, it might be possible to remove a benign tumor of the heart. However, few, if any, are ever referred to the experienced thoracic surgeon. An intrapericardial teratoma was successfully removed by Beck.

### Prognosis

The prognosis of benign tumors of the mediastinum is excellent. The prognosis of the malignant teratoid tumor, the neurofibrosarcoma, and the thymic carcinoma is invariably poor. It is possible for a patient with a small slowly growing mediastinal tumor to live for a long period of time and, in fact, die from some unrelated cause if the tumor does not cause cardiac embarrassment. Patients with malignant primary tumors of the heart are hopeless.

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carcinoma of the breast (particularly from the inner quadrants) not too rarely produce voluminous mediastinal masses. If the primary carcinoma is relatively small and not easily discernible, then the presence of a large mediastinal mass may be thought primary rather than metastatic.

The tumors which arise from the chest wall, such as *chondromas* and *chondrosarcomas* (costal cartilage origin), may project into the anterior mediastinum. *Mesotheliomas of the pleura* may also cause confusion in diagnosis because of their spread to the anterior mediastinum. Even tumors of the spinal cord may extend into the mediastinum.



Fig. 356.—Innumerable metastatic nodules both pigmented and nonpigmented within the myocardium from a widely disseminating malignant melanoma. (Specimen contributed by Dr. Robert A. Moore, Department of Pathology, Washington University School of Medicine, St. Louis, Mo.)

*Metastases to the heart* may occur from any widely disseminating malignant tumor and are far more common than primary tumors in this organ. The diagnosis has been made in about ten cases (Strouse). Direct invasion of the heart itself most frequently occurs from primary carcinoma of the lung or esophagus. Melanocarcinomas are particularly prone to involve the myocardium terminally, and in any post mortem series about 50 per cent will show involvement (Moragues) (Fig. 356). Metastatic lesions occur most frequently in the region of the right auricle (Strouse).

#### Treatment

Procrastination and watchful waiting are contraindicated in the handling of mediastinal tumors. A benign mediastinal tumor has a good chance of becoming malignant, and other complications may develop which can cause death.



## Chapter X

# CANCER OF THE DIGESTIVE TRACT

### CARCINOMA OF THE ESOPHAGUS

#### Anatomy

The esophagus is a muscular tube extending from the lower border of the cricoid cartilage to the stomach and having an average length of 25 centimeters. Its limits correspond to the level of the sixth cervical vertebra and the tenth or eleventh dorsal vertebrae. Anteriorly its lower end corresponds to the junction of the seventh rib cartilage with the sternum. There are three important areas of anatomic constrictions of the esophagus. The first, at the level of the cricoid is the narrowest and most rigid and extends about 15 centimeters. The second is the longest, extending 4 to 6 cm., with two points of constriction, one where the aorta crosses in front of the esophagus and the other where the left main stem crosses. The third is a diaphragmatic constriction measuring 1 to 2 cm. in height.

The anterior surface of the cervical esophagus is in contact with the trachea. In the thorax it is placed deep in the posterior mediastinum, separated from the spine by the muscles. Laterally it is in relation on the right side with the azygous vein and the pleura and on the left with the recurrent nerve, the common carotid, the subclavian artery, the thoracic duct, and the aortic arch. After the crossing of the bronchus at the level of the fourth or fifth dorsal vertebra, the esophagus progressively becomes separated from the spine by the descending aorta and also by the thoracic duct and the azygous vein. The vagus nerves take a lateral position to the esophagus. Anteriorly this lower thoracic portion of the esophagus is in relation with the pleura and left lung (Fig. 357).

**Lymphatics**—The two main lymphatic networks of the mucosa and submucosa and of the muscular layers of the esophagus gather on the external surface in three groups of lymphatic trunks: (1) the *upper trunks*, which end in the cervical lymph nodes along the internal jugular vein and in the supraclavicular lymph nodes, (2) the *middle trunks*, which end in the posteromedial lymph nodes and in the retrotracheal lymph nodes, and (3) the *lower trunks*, which go to the lymph nodes of the cardia and to those of the lesser curvature of the stomach (Fig. 358).

There is a rich intercommunication between the mucosal, submucosal, and muscular lymphatic networks. They may extend directly from the mucosa or the submucosa or from the muscularis to the closest node, or the collecting vessels in the submucosa may ascend or descend in the muscularis and then traverse it to empty into nodes. The collecting vessels in the muscularis parallel this. In other words, the lymphatic vessels from any one segment of the esophagus may drain directly into the closest node or empty into nodes at considerable distance either above or below the lesion.

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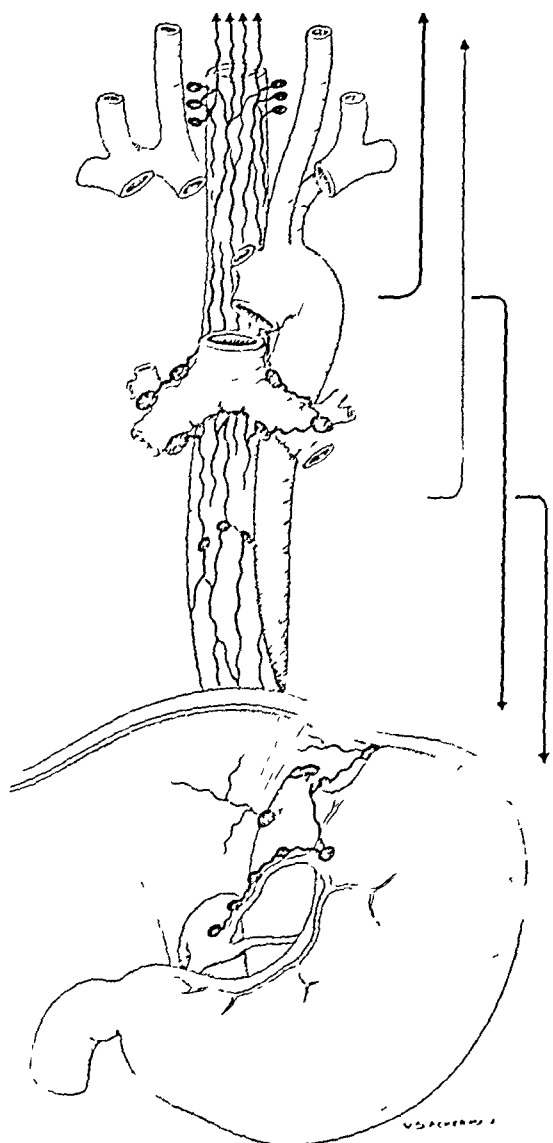


FIG. 58.—Anatomic sketch of the lymphatics of the esophagus demonstrating the cervical, the mediastinal, and the subdiaphragmatic lymph nodes. The curved arrows indicate the possible areas of drainage to and the cervical or subdiaphragmatic region. The chance of subdiaphragmatic spread increases from the upper third downward.

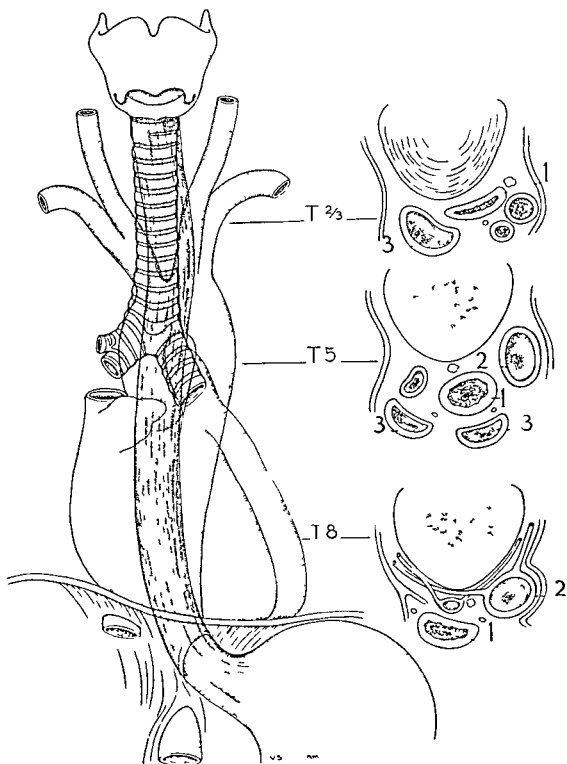


Fig 33.—Anatomical sketch of 1 the esophagus showing its relations to 2 the aorta and 3 the tracheobronchial tree. The cross sections give levels of the spine demonstrating the intimate relation of the esophagus to the other structures.

ulcerated and spread in surface without much obstruction. Not infrequently they extend over a wide area (10 cm or more). Submucosal infiltration may sometimes be the cause of pallor of the mucous membrane and a verrucous appearance. The tumor may be associated with considerable formation of connective tissue, and for that reason is designated as scirrhous. Mathews, in a review of 237 autopsies of patients with cancer of the esophagus, found twenty-two with no obstruction (Fig 360). These lesions usually show deep

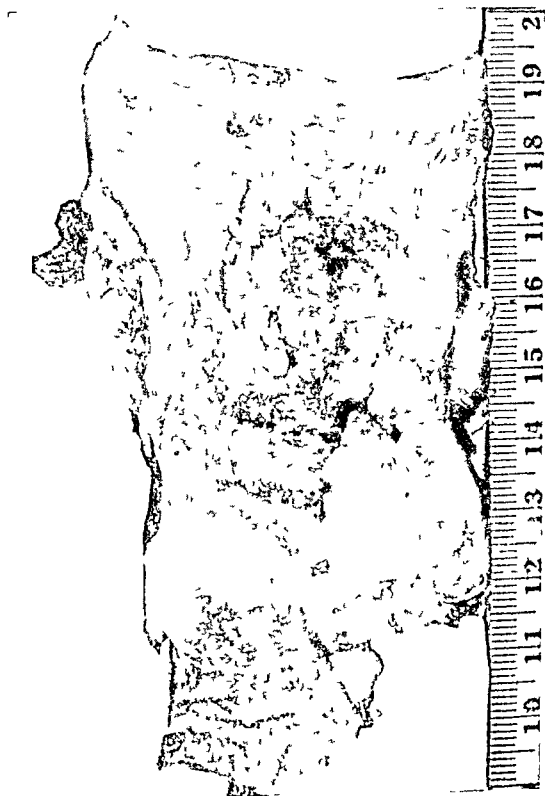


Fig 359—Surgical specimen of deeply ulcerating constricting undifferentiated carcinoma of the esophagus. Pathologic examination revealed metastases to many regional lymph nodes and death followed from distant metastases within a year.

ulceration with even dilatation of the lumen. More often, however, as the obstruction of the esophagus progresses, a compensating dilatation which may reach tremendous proportions occurs on the segment of normal esophagus proximal to the tumor. Because of the lack of serosal covering of this organ, the ability of tumors to spread outside of it is enhanced, and because of the intimate association of the esophagus with important structures within the thorax, various organs may be directly invaded even at an early stage of the

### Incidence and Etiology

In the year 1940 there were 2,804 deaths from carcinoma of the esophagus in the United States (*Vital Statistics*). Death from this form of cancer makes up approximately 2 per cent of all deaths from cancer in the United States. Dormanns collected statistics from forty-two German institutions between 1925 and 1933 in which there was a total of 22,139 autopsies in cases of cancer, the most common locations of cancer found were in the following order: stomach, lung, rectum and esophagus. There were 1,679 cases (7 per cent) of carcinoma of the esophagus. This form of cancer seems to prevail in China where it makes up about one-half of all neoplasms of the alimentary tract if tumors of the oral cavity are excluded (Kwan, 1937). There also seemed to be a prevalence of this form of cancer in Negroes in Curaçao, for in 650 autopsies performed by Hartz, the most common form found was cancer of the esophagus, the second most common being carcinoma of the stomach.

Cancer of the esophagus is most often found in individuals 40 to 60 years of age (75 per cent of all cases). In females the peak incidence occurs at a slightly younger age. Guisez (1935) found a relation of 5 men to 1 woman in a study of 565 cases. This predominance in males is even greater in the Chinese: of fifty-nine patients reported on by Lang, fifty-six were males and only three were females. The average age was 54 years. By contrast, Ahlbom has reported that 40 per cent of carcinomas of the esophagus in Sweden are found in females.

Oral infections, rough character of the food, heavy consumption of strong wines (China), habit of drinking hot tea (Scotland), and strong alcoholic drinks (Russia, Japan) have been thought to play a role in the etiology of this form of cancer (Wu, Kwan, Watson, Turner). Syphilis is rarely considered of any etiologic significance. Tomlinson (British West Indies), however, found a considerable proportion of syphilis with carcinoma of the esophagus; diverticula are rarely the site of origin of a carcinoma of the esophagus (Berard and Sargnon). Carcinoma can develop in a long-standing stricture. Benedict collected thirty-three such cases, sixteen of which were due to ingestion of lye. Rake reported on fifteen patients with achalasia, in three of whom carcinoma developed. This was an unusually high incidence for Plummer and Vinson saw none in 301 patients with achalasia, and of 207 seen by Bersack only one developed carcinoma of the esophagus. In Sweden, Ahlbom attributed the greater proportion of carcinoma of the esophagus in women to the frequent occurrence in this sex of Plummer-Vinson's syndrome (sideropenia), which is frequent in the underprivileged women of that country.

### Pathology

**Gross Pathology**—Carcinoma of the esophagus may arise in the upper, middle, or lower third. Ochsner collected 8,572 cases of cancer of the esophagus from the medical literature and found that 20 per cent developed in the upper third, 37 per cent in the middle third, and 43 per cent in the lower third.

Some carcinomas of the esophagus develop in the form of a bulky fungating growth which rapidly closes the lumen (Fig. 359), others are superficially

TABLE XI INVASION OF VARIOUS ORGANS BY CARCINOMA OF THE LUNG AT DIFFERENT LEVELS  
(From Dormanns, E. Ztschr f Krebsforsch, 1930)

	LARYNX	THYROID GLAND	AORTA AND GREAT ARTERIES	TRACHEA AND BRONCHI	PLEURAL CAVITY	GREY MATTER	LUNG AND HILUS	PERI CARDIUM	VERT BR	DIA- PHRAGM AND PERI TONFUM	LIVER
Upper third	122	15	4	90	5	1	0	0	0	0	0
Middle third	358	0	25	216	15	7	65	13	6	0	0
Lower third	154	0	10	35	24	1	38	16	0	6	5
Total	634	15	39	341	44	11	103	29	6	6	5



Fig. 300.—Autopsy specimen of a polypoid nonobstructing undifferentiated carcinoma of the esophagus in a patient operated on for a metastatic brain lesion thought to be primary brain tumor. The primary lesion was not clinically suspected. (Specimen contributed by Dr. Robert A. Moore, Department of Pathology, Washington University School of Medicine, St. Louis, Mo.)



TABLE XI INVASION OF VARIOUS ORGANS BY CARCINOMA OF THE ESOPHAGUS AT DIFFERENT LEVELS  
(From Dormanns, E. Ztschr f Krebsforsch, 1939)

	PANAS	THYROID GLAND	AORTA AND GREAT ARTERIES	TRACHEA AND BRONCHI	PLEURAL CAVITY	GREAT VEINS	LUNG AND LUNG HILUS	PERI- CARDIUM	VERTP BR AF	DIA PHRAGM AND PERI TONEUM	LIVER
Upper third	122	12	15	4	90	5	3	0	0	0	0
Middle third	338	0	0	23	216	15	7	65	13	6	0
Lower third	154	0	0	10	35	24	1	38	16	0	5
Total	634	12	15	39	341	44	11	103	29	6	5

disease (Table XI) Tumors of the upper third of the esophagus may involve the carotid arteries, pleura, the recurrent laryngeal nerves, and the trachea Tumors of the middle third may invade the left main stem bronchus the thoracic duct, the aortic arch, the subclavian artery, the intercostal arteries, the azygous vein, and the right pleura Tumors of the lower third may invade the pericardium, the left auricle, the left pleura and the descending aorta In addition, the tumor may simply spread into the mediastinum, producing a mediastinitis, or extend to the pleura and lung and be the cause of empyema Invasion of a large artery may occur and, interestingly enough veins are less frequently perforated than the arteries and are more usually effaced by compression (Berard and Sargnon)

Necrotizing bronchopneumonia and gangrene are very commonly found because of the frequent invasion of the trachea, left main bronchus and the lung itself

Very rarely *benign tumors* of the esophagus may be encountered more frequently in male than in female patients (Patterson Adams [1945 1943], Harrington) These tumors may arise from the smooth muscle (most common), fat connective tissue, blood vessels epithelium, or glands Depending on the tissue from which they arise they may be intraluminal or intramural Very rarely they undergo malignant change (French) When they become very large they may obstruct the lumen and become ulcerated and secondarily infected

**METASTATIC SPREAD**—In the upper third of the esophagus dissemination through the lymphatics may lead to lymph nodes of the anterior jugular chain or of the supraclavicular region Tumors of the middle third may metastasize to the mediastinum but also to the subdiaphragmatic lymph nodes Tumors of the lower third metastasize predominantly to abdominal lymph nodes In a study of seventy two cases of carcinoma of the esophagus, Churchill (1942) found only one of twenty four cases of carcinoma of the upper third which metastasized to the subdiaphragmatic lymph nodes, while eleven of thirty two carcinomas of the middle third presented abdominal metastases and eight of sixteen cases of the lower third were found to metastasize to the subdiaphragmatic lymph nodes Metastases through the blood vessels may occur Tumor emboli enter the caval system and are the cause of direct pulmonary metastases Mediastinal lymph nodes may secondarily invade any of the surrounding structures Distant metastases to liver bones and kidneys are not infrequent Table XII illustrates the distribution of lymph nodes and distant metastases in relation to the level of origin of the carcinomatous lesion

**Microscopic Pathology**—The overwhelming majority of carcinomas of the esophagus are epidermoid usually rather undifferentiated Broders reviewed 207 cases and found the following distribution by grades

GRADE	NUMBER OF PATIENTS	PERCENTAGE
I	0	
II	16	8
III	95	45
IV	96	46

Epidermoid carcinomas of the esophagus are, as a rule much less differentiated than carcinomas of the oral cavity and they metastasize earlier. Their submucosal spread may be recognized only microscopically.

TABLE XII DISTRIBUTION OF METASTASIS ACCORDING TO THE LEVEL OF ORIGIN OF CARCINOMA  
(From Dormanns, E. *Ztschr f Krebsforsch* 1930)

ORGANS	UPPER THIRD (121)	MIDDLE THIRD (418)	LOWER THIRD (285)	ALL (824)
Lymph nodes				
Suprclavicular	6	20	12	38
Infrclavicular	1	5	1	7
Peritacheal and peri- esophageal	84	99	37	220
Mediastinal	28	231	147	406
Abdominal	11	104	121	236
Liver	20 (16%)	122 (29%)	122 (43%)	264 (32%)
Lungs and pleura	28 (31%)	82 (20%)	56 (20%)	176 (21%)
Bone	11 (9%)	31 (7%)	26 (9%)	68 (8%)
Kidneys	5	30	24	59
Omentum and peritoneum	2	15	27	44
Suprarenal glands	4	10	21	35

It is questionable whether adenocarcinomas of the esophagus constitute an entity. They usually occur in the lower third near the cardia and in practically every instance represent an upward extension of primary adenocarcinoma of the stomach.

### Clinical Evolution

The early symptoms of carcinoma of the esophagus may be so trivial that they cause no alarm. There may be a sensation of pressure, substernal distress and a sensation of fullness. As the disease progresses *dysphagia* appears and is the most constant symptom throughout the course. *Dysphagia* was the initial symptom in 649 of 671 cases of carcinoma of the esophagus reviewed by Jackson (1925). It may be progressive and the patient unconsciously becomes more thorough in the mastication of food and gradually changes to a soft or liquid diet. Hurried eating also causes a sensation of obstruction. The *dysphagia* may appear suddenly due to spasmodic obstruction above the tumor. Later the obstruction disappears and the *dysphagia* improves, but repeated episodes may be noted throughout the evolution of the disease. It may reach the point where not even liquids can pass by the obstruction. With the *dysphagia* there may be some regurgitation due to accumulation of saliva and mucus in the dilated portion of the esophagus just above the tumor. It is sometimes accompanied by elimination of a fragment of tumor and slight hemorrhage. As a consequence of *dysphagia* and in spite of the fact that the patient is usually ravenously hungry, a rapid *weight loss* inevitably follows. This weight loss is usually in disproportion with the extension of the tumor for it is only due to dehydration and insufficient assimilation of food and not necessarily to wide dissemination of the disease. *Pain* may be present, but this is a less constant symptom. It may be felt diffusely below the sternum or it may spread toward the pharynx, neck, or ear. This may be due

disease (Table XI) Tumors of the upper third of the esophagus may involve the carotid arteries, pleura, the recurrent laryngeal nerves, and the trachea Tumors of the middle third may invade the left main stem bronchus, the thoracic duct, the aortic arch, the subclavian artery, the intercostal arteries, the azygous vein, and the right pleura Tumors of the lower third may invade the pericardium, the left auricle, the left pleura, and the descending aorta In addition, the tumor may simply spread into the mediastinum, producing a mediastinitis, or extend to the pleura and lung and be the cause of empyema Invasion of a large artery may occur and, interestingly enough, veins are less frequently perforated than the arteries and are more usually effaced by compression (Berard and Sargnon)

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II	16	8
III	95	45
IV	96	46

third there may be a forward displacement of the trachea and supraclavicular or cervical adenopathy

**Laryngeal Examination**—Examination of the larynx should be done in all patients suspected of having carcinoma of the esophagus, for it may reveal a hemiparalysis of the larynx because of compression of the recurrent laryngeal nerve. Not too infrequently this paralysis may be bilateral.

**Bronchoscopic Examination**—A bronchoscopic examination should be carried out in every patient with carcinoma of the esophagus, particularly if operation is contemplated (Bud). It may reveal external deformity of the trachea or left main bronchus due to external compression by the tumor, and not too rarely it will show invasion of these structures and a resulting fistula.

**Esophagosopic Examination**—Esophagoscopy is indicated in every patient complaining of some disturbance in swallowing, and particularly when the patients are over 40 years of age. McMillen reported 878 esophagoscopies in patients complaining of difficulty in ingestion of food not due to a foreign body and found 350 (40 per cent) presenting carcinoma of the esophagus. The esophagosopic examination is without danger in experienced hands, but there is unquestionable danger of perforation, particularly in the presence of tumor.

The esophagosopic examination may reveal little or no obstruction, but in the majority of cases the lumen will be narrowed by a fungating or sclerotic tumor. The examiner should notice the presence or absence of fixation of the esophageal wall. In general, the location of the tumor is expressed in centimeters of distance from the dental arch. The upper limits of the tumor, however, may give an entirely erroneous impression of the actual level of the tumor, for it usually spreads considerably in surface away from its point of origin.

#### **Roentgenologic Examination —**

**Radioscopic Examination**—A radioscopic examination should always precede the taking of roentgenograms and is at times considerably more eloquent. When the patient swallows a small amount of thick barium meal, there is a short delay at the level of the cricopharyngeus, and then it falls in the form of a continuous stream and passes rapidly into the stomach. In the presence of an obstruction, the barium falls sluggishly and stops at the level of the constriction. In carcinoma of the esophagus, as Souttar has so succinctly stated: "There may be a very moderate degree of dilatation above, giving a solid shadow which terminates in a cone pointing downward, and from the apex of this cone a fine twisted stream of barium can be seen threading the tortuous channel of the growth" (Fig 361). If there is a stenotic obstruction, the barium may stop at the point altogether and pass no further. The examination may have to be repeated after the administration of antispasmodics. If there is a bronchoesophageal fistula, the barium usually passes into the bronchial tree and causes cough. In lesions of the lower third of the esophagus in the region of the cardia (Fig 362) the barium may conceal the lower limits of the tumor. In these instances the filling of the stomach with gas (effervescent beverages) may help in observing the irregularities in the region of the cardia.

to direct invasion of the vagus nerve (Hoover) As a consequence of compression of the recurrent laryngeal nerve there may also be a *hemiparalysis of the larynx* In advanced cases there may be a *fetid odor*, usually emanating from alimentary fermentations in the large esophageal dilatation which takes place above the tumor In some instances there may be *sialorrhea* This excessive excretion of saliva has been attributed to a reflex due to the esophageal obstruction

*Cough* may appear because of regurgitation of food into the tracheobronchial tree More often, however, the cough appearing at the time of ingestion of food may be due to a tracheobronchial fistula Because of pulmonary complications, *fever* may also appear Development of necrotizing bronchopneumonia, empyema, mediastinitis, or hemorrhage from a large thoracic vessel leads to acute manifestations related to these conditions

The rapid loss of weight leads to asthenia and somnolence which rapidly may turn to cachexia Patients may die of starvation, but more often death occurs from one of the numerous complications mentioned Very rarely a carcinoma of the esophagus may give no local symptoms and be discovered only because of its metastases (Fig 360)

The clinical evolution of *benign tumors* is usually much slower than that of malignant lesions As they increase in size they may produce dysphagia, and when they become ulcerated they may spontaneously bleed When the tumor occurs in the upper third of the esophagus and is pedunculated, its great mobility and the elongation of the pedicle may allow regurgitation into the oral cavity According to Adams (1943) "The behavior of the tumor may be terrifying to the patient, as it appears in the mouth as an oyster like mass during an attack of retching and quickly disappears without trace into the unknown regions from which it came"

### Diagnosis

The early symptoms of carcinoma of the esophagus are so trivial that as a general rule the complaints are disregarded even by the physician An early diagnosis is only possible when the complaints of cervical, retrosternal, or epigastric abnormal sensation is not regarded as a neurosis (Jackson, 1925) Very frequently there is a sensation of pressure or substernal distress or a sensation of fullness which is often diagnosed as a neurotic disorder or globus hystericus On the other hand, if a thorough examination is done only in cases which present a clear clinical picture, then as a rule the carcinoma is no longer in an early stage A spasmodic obstruction of the esophagus is frequently diagnosed as a foreign body

In general a case report of the history and development of symptoms is of value and it should not be forgotten that although a progressive dysphagia is the classical symptom, the sudden attacks of dysphagia may very well represent an early carcinoma of the esophagus The inspection often only contributes details of the emaciation and dehydration In tumors of the upper

that a *posterioid carcinoma* (more frequent in females) may invade the upper fourth of the esophagus and be considered as a lesion of this organ. Also very frequently *adenocarcinomas of the stomach* invade the lower third of the esophagus. The differences are only of academic importance for purposes of classification. *Metastatic lesions* secondarily involving the esophagus are rather infrequently observed. Toreson reported twenty-six such instances from primary lesions in the bronchus, stomach, larynx, breast, etc.



Fig. 362.—Roentgenogram of an adenocarcinoma of the terminal portion of the esophagus and cardia showing typical filling defect and dilatation of the esophagus above the lesion.

*Achalasia*, a functional abnormality, offers the greatest difficulty in differential diagnosis because of obstruction and dilatation of the esophagus which seem identical with those of carcinoma (Fig. 363). *Achalasia*, however, occurs in younger individuals and is often associated with hypertrophic gastritis. The history of dysphagia may be considerably longer, and because of retention of food and chronic irritation there may be marked chronic esophagitis. Very rarely a carcinoma of the esophagus may develop in a patient with achalasia.

*Radiographic Examination*—A permanent record of the roentgenologic findings is, of course, always desirable. It might be easier in the differential diagnosis to study certain irregularities on the film and to compare them with previous studies. Moreover, the roentgenograms help in establishing evidence of a tumor shadow around the obstruction and in marking the limits of the lesion when treatment is contemplated. The radiographic examination is also of value in establishing evidence of mediastinal and pulmonary metastases.



Fig. 361.—Roentgenogram of a carcinoma of the midportion of the esophagus showing typical dilatation of the esophagus above the lesion ending in a cone and revealing the tortuous course of the barium at the level of the tumor.

**Biopsy**—At the time of esophagoscopy a specimen should be removed for microscopic examination. This is not always possible or easy, for in the scirrhous type of lesion there may be edema of the overlying mucosa with hypertrophy of the muscularis (Lindsay). Because of the difficulties in removing the material and the inaccuracies due to the limitations of monocular endoscopic view, a negative biopsy is of no value and is only an indication that a new specimen should be removed.

**Differential Diagnosis**—In establishing a differential diagnosis of carcinoma of the esophagus with other forms of tumor it should be remembered



the tumor area, which has not interfered with the elasticity of the esophageal wall. No matter how large the benign tumor, the barium will flow smoothly and evenly around it and on the opposite side of the wall. *Aortic aneurysms* may compress the esophagus. Evidence of this compression will be clear on roentgenologic examination because of the site and shape of the compression and the



Fig 364—Roentgenogram of a diverticulum of the upper third of the esophagus showing retention of opaque material in the pouch

displacement of the esophagus. *Mediastinal cysts* and *metastatic nodes* from carcinomatous lesions elsewhere may also give an extrinsic deformity of the esophagus, but here, as in the preceding example, the mucosal pattern will not be modified and there will be no evidence of irregularities. Diverticula may also result in dysphagia, but here the differential diagnosis will be easily solved on roentgenologic examination (Fig 364). *Foreign bodies* are easily seen because of their density or because they become coated with barium.

(Rake) *Esophageal varices* occurring at the terminal portion of the esophagus may present a stenosis followed by irregularities, but these usually have a regular pattern and are associated with other lesions such as cirrhosis of the liver. *Peptic ulcers* of the terminal portion of the esophagus may be the cause of stenosis but usually are easily diagnosed.



Fig 363—Roentgenogram in a case of achalasia. Note extreme dilatation with puddling of barium.

*Benign tumors* may present a problem of differential diagnosis, but it should not be forgotten that only about 100 of these cases have been reported in the medical literature. The radioscopic examination demonstrates the presence of these clearly delimited tumors with peristaltic waves invariably passing through

erly chosen. Smithers (1943), using 400 kv equipment and a special optical device for the alignment of the beam of radiations (Mayneord), treated forty-four patients, thirty-two of whom received a complete series of treatments. In thirty there was marked alleviation of the symptoms. Nielsen, in reviewing a large series of patients who were treated at the Roentgen Station of Copenhagen from 1913 to 1938, concluded also that patients in good general condition with localized tumors are easily relieved of obstructive symptoms, and that they gain weight and experience marked subjective improvement. Later Nielsen has advocated the use of rotation therapy of carcinoma of the esophagus, particularly when it arises within the intrathoracic portion. He feels that this would be of the greatest value when supervoltage therapy is used. This technique has the advantage of increasing the depth dose in relation to a more widely distributed skin dose, thus minimizing the untoward effects on normal structures. The procedure, however, has the disadvantage that lymph node metastases not demonstrable on roentgenographic examination may not be in the center of the field of irradiation.

When external roentgentherapy is chosen as the form of treatment, a previous gastrostomy is sometimes useful for it allows the patient to recover strength and to maintain a good intake throughout the treatment. This also eliminates the trauma of the passage of food and possibly diminishes the possibilities of perforation. However, a previous gastrostomy is not always necessary and, in many instances, can be avoided. In advanced cases, however, when the treatment is undertaken for mere palliation and where a gastrostomy will finally be required, it might as well be done before the beginning of treatments.

**SURGERY** —In 1913 Torek successfully resected a carcinoma of the thoracic portion of the esophagus and constructed an artificial tube connecting the esophagus to the stomach. The patient lived for thirteen years and died of intercurrent disease without evidence of recurrence. This successful instance stimulated surgeons to consider carcinoma of the esophagus as an operable disease. It is only in the last decade, however, that notable advances in surgery of carcinoma of the esophagus have occurred. These advances are due to the efforts of such men as Phemister, Adams, Garlock, Ochsner, Turner, Sweet, Churchill, and many others. These advances consist mainly of a better knowledge of chest physiology and the elimination of major complications with consequent reduction of the operative mortality. A better knowledge of the mechanism of shock and the means of avoiding it, as well as the advent of the sulfonamides and penicillin and their role in the control of infections, have also contributed to this reduction of operative mortality. It should be pointed out that surgery of carcinoma of the esophagus is now concerned with its radical removal, including node-bearing areas—a fundamental concept of surgery of cancer.

The number of lesions suitable for a surgical removal is very small, usually because of the extension of the disease, the general condition of the patient, his age, and the presence of abdominal or cervical metastasis. The duration

### Treatment

The treatment of carcinoma of the esophagus is still in an active state of evolution from its radiotherapeutic as well as from its surgical standpoint. It is true that in the past radiotherapy has offered merely palliation and also that a surgical excision has been considered a heroic procedure, but at present new systematic and thorough studies in the application of high voltage radiations have contributed encouraging results and the development of thoracic surgery has brought about the possibility of successful excision of these tumors.

**CURIETHERAPY**—Treatment of carcinoma of the esophagus by means of interstitial implantation of radium through the esophagoscope was abandoned early because of its systematic failure. Treatment by means of a radium bougie introduced in the lumen of the esophagus has also frequently been a failure. Some meticulous workers, however, have succeeded in obtaining long time survivals by means of protracted curietherapy in a selected group of cases (Guisez). The failure of this form of treatment, however, is easily understandable. Radium tubes within the lumen of the esophagus are unable to achieve homogeneous irradiation of a tumor which may be eccentrically placed around the lumen. In addition this form of treatment is usually accompanied by a rapid melting of the tumor and perforation of the esophagus, resulting in fatal complications (Zuppingen). Obviously in the presence of a metastatic adenopathy even within the mediastinum, and this is frequently the case, the treatment is condemned to failure.

**ROENTGENTHERAPY**—Irradiation of a carcinoma of the esophagus by means of external roentgentherapy presents several difficulties. The tumor is deeply situated and can only be reached after passing through important vital structures such as the lung, the heart and the large vessels of the thorax. In addition even though the radiographic examination may furnish good information as to the topography of the tumor usually somewhat distant nodes are invaded and the fields of irradiation are necessarily large. Irradiation through large fields results in systemic and marked local reactions when a large daily dose is administered. This leads to underdosage and consequently to nothing but temporary palliation. Carcinoma of the esophagus, however, is a radiosensitive and radiocurable form of tumor and an intelligent and well planned external irradiation should succeed in permanently sterilizing at least a small number of these cases. High voltage equipment of 800 to 1000 kv. contributes a more penetrating form of radiations which should be very useful in the treatment of this deeply situated cancer. In addition proper focusing of the tumor, choice of dimensions of field, proper evaluation of depth dosage and above all carefully protracted administration of radiations are basic conditions to the obtention of results.

Watson demonstrated with a series of twenty one cases of carcinoma of the esophagus the possibilities of superior roentgentherapy. He feels that a sufficient dosage can be delivered with high voltage equipment and that better results can be obtained if certain conditions are observed.

thrombosis (Garlock, 1944) It may be expected that this operative mortality will become lower with the advances of thoracic surgery

*Benign tumors* of the esophagus should be treated by surgical removal If they are pedunculated and intraluminal, they may be removed by snare, preferably at the time of the first esophagoscopy If they are larger or intramural, an esophagotomy may be necessary (Harrington) In more advanced cases, partial esophagectomy will be required

### Prognosis

The average life expectancy of patients with carcinoma of the esophagus is very short In 299 *untreated patients with carcinomas* of the esophagus, Greenwood reported that 25 per cent were dead within six months, 50 per cent within eight months, and 75 per cent within a year According to Adams, the average time between first symptom and death ranges between five and eight months This duration is apparently not influenced by the age of the patient, the location of the lesion, or the type of tumor

Patients with carcinoma of the esophagus who receive *palliative treatment* in the form of intubation, gastrostomy, etc., have very little prolongation of life except perhaps in a few instances The results of *curietherapy* have been so poor that this form of treatment has now been almost generally abandoned Guisez, however, reported eleven patients surviving more than three years in a series of 270 treated by radium bougie

In the past, the results of *roentgentherapy* have been very poor Nielsen reported on a large series of patients treated between 1913 and 1938, most of whom received an insufficient amount of radiations, for purposes of pure palliation However, in seventeen cases in which he attempted the delivery of an adequate tumor dose, eight patients survived more than one year and two were alive and symptom free at the end of two and one-half and three and one-half years More recently Nielsen has treated another group of patients with a technique called "rotation therapy" A large number of these patients became free of symptoms and were generally improved Twenty-five per cent were alive after one year and 15 per cent were alive after two years Smithers reported forty-four patients treated for carcinoma of the esophagus with external roentgentherapy at the Royal Cancer Hospital of London Thirty-two of these patients completed the treatment, thirty had marked alleviation of symptoms, fourteen lived more than one year, and five lived beyond two years following treatment After a review of the literature, Smithers (1944) found ten patients with carcinoma of the esophagus surviving five years after roentgentherapy In twenty-one patients treated by Watson with "supervoltage" *roentgentherapy*, there was marked symptomatic improvement in eleven patients, and one patient remained without symptoms for more than thirty months Buschke reported on a series of ten patients with carcinoma of the esophagus treated with "supervoltage" roentgentherapy, only five of whom were given an adequate dosage, with one patient surviving three and one-half years after treatment Jacobsson reported on a patient with carcinoma of the lower third of the

of the symptoms is often of little value in deciding on the operability of a case. The presence of a laryngeal paralysis, bronchoscopic evidence of invasion of the bronchus or trachea, the finding of a rectal shelf, and a bad general condition are definite contraindications to surgical excision. Obese individuals of short stature have a high operative mortality. The presence of pain invariably means invasion of contiguous structures and probable inoperability. Tumors located between the levels of the aortic arch and the left main stem bronchus rapidly invade and become fixed to these structures and for this reason are practically never operable. Tumors most amenable to the surgical excision are those located in the mid and terminal thirds of the esophagus. They constitute approximately 80 to 85 per cent of all carcinomas. However, in tumors near the terminal third of the esophagus, the percentage of those with abdominal lymph nodes is greater, and this is also an important contraindication to the operation. This finding may be established in a preliminary exploratory laparotomy. At the time of exploration of the chest, if the tumor is partially or completely fixed, the operation is contraindicated and attempt at removal, even if momentarily successful, invariably results in quick recurrence. Involvement of the right mediastinal pleura, however, does not necessarily mean inoperability. This brief resume of contraindications of surgical excision for carcinomas of the esophagus explains why so few patients are eligible for this form of treatment. Of thirty patients with carcinoma of the midportion of the esophagus reported on by Sweet, fifteen presented abdominal metastases and esophagectomy was possible in only eight. Of 100 consecutive cases of carcinoma of the esophagus reported by Adams, only 28 could be explored and of these only 16 could be resected.

The technique for surgical removal of the *upper third* of the esophagus has not yet been definitely established. There have been a few cases, however, of radical resection of the upper third together with the larynx and associated cervical lymph nodes which have been done with success (Eggers). In the past, tumors of the *midportion* of the esophagus have been economically resected in order to facilitate the construction of an artificial esophagus under the soft tissues of the chest in an attempt to connect the remaining upper portion of the esophagus and a gastrostomy opening. This form of treatment, even when successful, has been quite unsatisfactory. In addition, this usually implied a poor operation for the removal was not usually sufficiently large. Phemister and Sweet resect the entire esophagus below the level of the aortic arch and complete the operation by an esophagogastric anastomosis within the chest. This brilliantly conceived operation permits the removal of the nodes below the diaphragm and permits normal nourishment. In carcinoma of the *lower third* of the esophagus a thoracoabdominal approach is used with removal of the terminal esophagus, the upper portion of the stomach, and the lymphatic node areas commonly involved. This is also followed by an esophagogastric anastomosis.

Sweet reported six operative deaths in twenty consecutive cases. The causes of death after surgery are related to infection such as empyema, pneumonia, peritonitis, fistulas, and accidents common in older patients such as pulmonary embolism, heart failure, respiratory failure, cerebral accidents, and coronary

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esophagus treated with roentgentherapy which was pathologically verified. The patient was alive and free from evidence of tumor more than six years after the treatment.

Although the results of *surgical treatment* have greatly improved, the percentages of long standing cures are very small. Adams (1944) reported a series of sixteen resected lesions, with three patients remaining alive for twelve, sixteen, and twenty five months following operation. He also reported on eight patients operated on for lesions of the midportion of the esophagus four of whom were living and well up to two years. Garlock (1944) reported on sixteen patients operated on for carcinoma of the esophagus, eight dying of a recurrence from nine months to two years following operation, one dying of coronary thrombosis, and seven remaining without evidence of disease (four of these for more than three years).

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to cancer of the stomach in different countries. Carcinoma of the stomach as well as gastric ulcers are very infrequent in Egypt where Dolbey saw only eight cases in three years.

*Gastric polyposis* is a rare lesion but an unquestionably precancerous one in a high percentage of cases. In thirty-seven cases reported by Pearl (1913), nineteen (50 per cent) showed evidence of malignant change. Stewart (1929) reported on twenty-seven patients with single polypi of the stomach, of whom six had associated carcinoma, and twenty patients with multiple polypi, seven of whom had cancer. It is, of course, impossible to determine how many carcinomas arise from polyps, but it would be reasonable to assume that such is the origin of some of the polypoid carcinomas.

There is a fairly high incidence of benign gastric tumors associated with *pernicious anemia*. In 151 post-mortem examinations on patients with pernicious anemia studied by Brown, 8 per cent presented gastric tumors. In another series of 293 autopsied cases of pernicious anemia, thirty-six (12 per cent) had carcinoma of the stomach (Kaplan). In 1939 Jenner reported on 181 living patients with pernicious anemia, 4 per cent of whom developed carcinoma, an incidence calculated to be twelve times greater than that of the rest of the population of the same age. Rigler (1945) reviewed 211 clinical cases of pernicious anemia in which extensive and repeated roentgenologic and gastroscopic studies were done (Table XIII). He felt that a definite relationship existed. It should be emphasized that the anemia which is coexistent with and often occurring after the development of carcinoma of the stomach should not be confused with pernicious anemia.

TABLE XIII PROPORTION OF BENIGN AND MALIGNANT TUMORS FOUND IN A STUDIED SERIES OF CASES OF PERNICIOUS ANEMIA  
(From Rigler, L. G., Kaplan, H. S., and Pink, D. L. I. A. M. A., 1945)

TOTAL CASES OF PERNICIOUS ANEMIA EXAMINED	CARCINOMA OF STOMACH	BENIGN TUMORS OF STOMACH	TOTAL TUMORS OF STOMACH
211	17 (8%)	15 (7%)	32 (15%)

The relationship of *chronic gastritis* to cancer is still extremely controversial. Konjetzny (1938) and Hurst (1929) believe that chronic gastritis is a definite precancerous lesion, Konjetzny believing that he can trace all gradations of change from chronic gastritis to carcinoma, and Hurst, that carcinoma never occurs in a normal stomach. The opposite viewpoint is maintained by Guiss and Stewart who, after carefully studying a large number of stomachs, concluded that there is no evidence to suggest a relationship except that the incidence of chronic gastritis increases with age and that chronic atrophic gastritis may be caused or intensified by the presence of carcinoma of the stomach. It is also true that the carcinomatous stomach may show absolutely no signs of gastritis (Guiss and Stewart). It is our opinion that the relationship between chronic gastritis and carcinoma is yet to be proved.

The relation of *chronic gastric ulcer* to carcinoma of the stomach is also debated, but the majority of writers believe that benign chronic gastric ulcers

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## CANCER OF THE STOMACH

### Anatomy

The stomach is a peritoneal organ situated in the left hypochondrial region and epigastrium. It is slightly flattened anteroposteriorly and thus it has a posterior and an anterior wall, a right lateral border (the lesser curvature) and a left lateral border (the greater curvature). From the esophageal opening called the cardia to the duodenal opening called the pylorus the stomach is arbitrarily divided into the fundus, the corpus, the pyloric antrum, and the pyloric canal. The stomach is attached, or rather suspended, by several peritoneal folds: the gastrohepatic ligament arising from the lesser curvature and the gastrocolic, gastrosplenic and gastrophrenic ligaments arising from the greater curvature.

The anterior relations of the stomach vary with the distention of the organ: they include the left lobe of the liver, the diaphragm and anterior abdominal wall. Posteriorly the stomach is in relation with the diaphragm, the spleen, the left suprarenal gland and kidney, the pancreas, the fourth portion of the duodenum, mesocolon, and, with distention, the transverse colon.

The arterial supply of the stomach is derived from the celiac axis. The lesser curvature derives its blood supply from the left gastric artery and the right gastric branch of the hepatic artery; the greater curvature is primarily supplied by the right gastroepiploic branch of the gastroduodenal artery and the left gastroepiploic and by the gastric branches of the splenic artery. The venous drainage of the stomach goes into the portal system directly or via the superior mesenteric and splenic veins.

The stomach is a muscular organ made up of an inner circular and outer longitudinal layer. It is covered on its surface by serosa and is lined by velvety mucosa thrown up into rugal folds. The gastric glands are densely arranged, penetrate the whole thickness of the mucosa, and contain four types of cells: the chief, parietal, mucous and argentaffin cells. The distribution of these cells varies in different portions of the stomach. Beneath the mucosa the submucosa contains abundant blood vessels, lymphatics and loose connective tissue.

**Lymphatics**—The stomach has several networks of lymphatics: the mucosal, the submucosal, the intermuscular and the subserosal networks.

carcinomas apparently arising on the basis of pre-existing ulcer and an increased number of small ulcerated or superificial carcinomas.

Carcinomas of the stomach usually arise in the pyloric region, pars media or the cardiac area. In 837 cases summarized by Oppolzer there were 456 in the pyloric region, 244 in the pars media, 61 in the cardiac area, 14 in the region of the greater curvature and in 62 instances the involvement was total.



Fig. 306.—Superficially spreading type of carcinoma of the stomach with superficial ulceration, wide submucosal extension and hypertrophy of the muscles of the pylorus. (Courtesy of Dr. A. P. Stout, Department of Surgical Pathology, Columbia University, New York, N. Y.)

**Superficially Spreading Carcinoma**—The superficially spreading type of carcinoma, or, as Gutmann designates it, the *mucosa en marche lente* is usually limited to the mucosa but can involve the submucosa. This lesion often originates near the pylorus and frequently is associated with irregular superficial scirrhous ulcerations which have been known to reach 5 or 6 cm. in diameter. The base of the ulcer has a diffuse reddish tint and the mucosa re-

show definite malignant degeneration in a small number of cases. The reasons for this belief lie in the clinical history, the roentgenologic examination, and, in particular, on the pathologic examination. Mallory presents the strongest dissenting opinion. He bases his conclusions mainly on histologic grounds and feels that carcinoma does not develop from an ulcer.

At autopsy, the advanced stage of the tumor in most instances precludes and obscures the evidence of its development from an ulcer. But when gastrectomies are done for chronic gastric ulcers, a variable number of carcinomas apparently developing on the basis of an ulcer are found. In a series of eighty-two cases of resected gastric carcinomas reported by Stout, eleven (13 per cent) had apparently developed at the margin of a pre-existing chronic ulcer. Of 300 consecutive gastrectomies on Gutmann's service, there were 85 papillary carcinomas, 133 benign gastric ulcers, 43 ulcers which had undergone malignant transformation, and 39 ulcerating carcinomas. Finsterer reported that in 15 per cent of his cases carcinoma was found to develop on the basis of a pre-existing chronic ulcer. The acute or subacute gastric ulcer, however, does not become cancerous.

Carcinoma of the stomach has been extremely difficult to produce in laboratory animals and many lesions reported as malignant were actually inflammatory or hyperplastic. It was not until 1942 that Stewart unequivocally produced adenocarcinoma in the pyloric area of the stomach in mice (strains C3H and I) by direct injection of methyleholanthrene into the wall of the stomach. Strong in 1943, by subcutaneous injection of methyleholanthrene produced adenocarcinoma of the stomach in the NIH mouse strain.

### Pathology

**Gross and Microscopic Pathology**—In practically all instances carcinoma of the stomach arises from mucus-secreting cells. It is an adenocarcinoma which, because of various growth characteristics and forms, takes on different patterns. Most clinicians, surgeons, and pathologists use a morphologic classification as this bears some relation to prognosis. The following modified classification is adapted from Boorman.

#### CLASSIFICATION OF CARCINOMA OF THE STOMACH

- Superficial spreading carcinoma (carcinoma in situ, *mucosa crosif à marche lente*)
- Gastric carcinoma arising from previous chronic ulceration
- Ulcerating carcinoma
- Polypoid carcinoma
- Polypoid carcinoma with moderate invasion
- Limits plastic
- Advanced carcinoma (no specific type)

The number of cases found in each category will, to a large extent, depend on the source of the material. If post mortem material is studied, a high percentage of cases will be of no specific type. If the surgical material is from a hospital in which the clinical staff is cancer-conscious, the roentgenologist is expert, and the surgical staff technically skilled and disposed to resect chronic gastric ulcers, this naturally will be reflected by an increased proportion of

carcinomas apparently arising on the basis of pre-existing ulcers and an increased number of small ulcerated or superficial carcinomas

Carcinomas of the stomach usually arise in the pyloric region pars media, or the cardiac area. In 837 cases summarized by Oppolzer there were 456 in the pyloric region 244 in the pars media 61 in the cardiac area 14 in the region of the greater curvature and in 62 instances the involvement was total

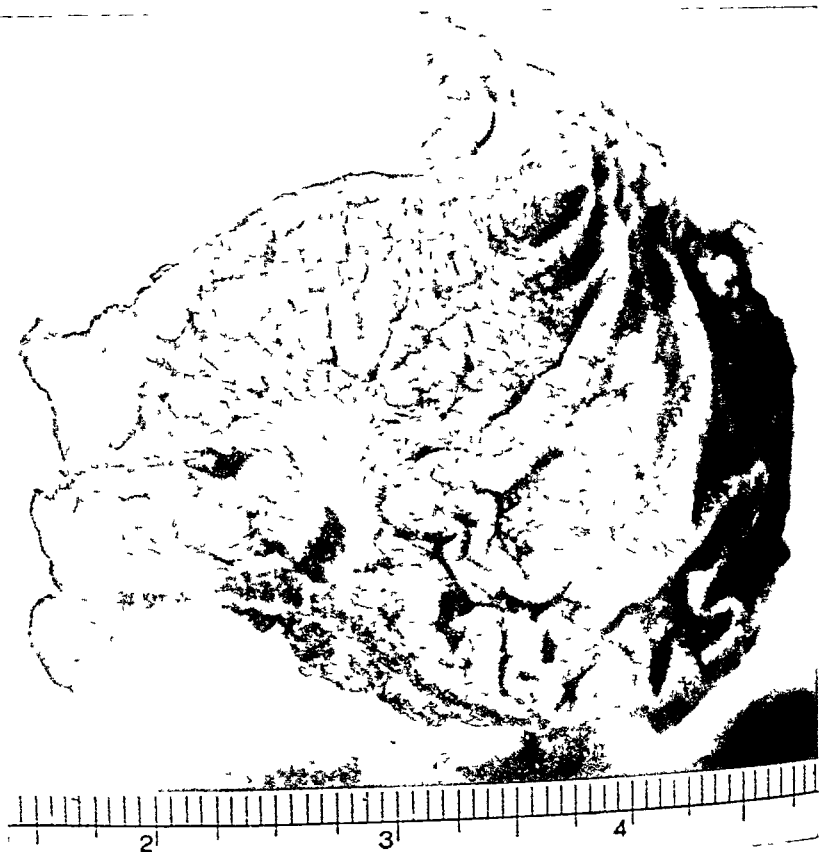


Fig 366—Superficially spreading type of carcinoma of the stomach with superficial ulceration wide submucosal extension and hypertrophy of the muscles of the pylorus. (Courtesy of Dr. A. P. Stout, Department of Surgical Pathology, Columbia University, New York, N. Y.)

**Superficially Spreading Carcinoma**—The superficially spreading type of carcinoma, or as Gutmann designates it, the *mucocrosis à marche lente* is usually limited to the mucosa but can involve the submucosa. This lesion often originates near the pylorus and frequently is associated with irregular superficial, serpiginous ulcerations which have been known to reach 5 or 6 cm in diameter. The base of the ulcer has a diffuse reddish tint and the mucosa fre

quently presents a slight nodulation. The pyloric ring muscles frequently show hypertrophy (Fig 366). The muscularis is not involved (Gutmann). It shows multiple microscopic areas of change in the overlying epithelium with disturbances of architecture and replacement by the glandular type of carcinoma. At times there is normal epithelium between the areas of disease which, as Mallory indicated, may have multiple foci of origin.



Fig 367—Advanced carcinoma of the stomach. Note replacement of the entire stomach by tumor with secondary invasion and metastases to the liver.

The two most common gross characteristics of the disease are first, its wide extension and, second, its superficiality (Stout). Externally the stomach appears normal and even when it is open there may be doubt as to the presence of tumor especially if there is no ulceration. Indeed it may not be recognized grossly even at autopsy. It is not known just how often carcinoma begins in this fashion. But superficially spreading carcinomas are seen with increasing frequency in clinics where patients are referred for early gastro-intestinal study and where surgical resection is frequently done. It is interesting that fifteen of 69 gastric tumors recently resected at the Presbyterian Hospital in New York were of this variety (Stout).

*Gastric Carcinoma Arising on the Basis of Previous Chronic Ulceration—*

We believe that a relatively small number of gastric ulcers can undergo carcinomatous changes and that the validity of such an assumption primarily depends upon the pathologic study. Benign chronic gastric ulcers occur on the lesser curvature and at the pylorus, while carcinoma is most frequently found in the prepyloric and cardiac areas. The typical chronic ulcer has punched-out well-defined margins with overhanging edges. Small benign chronic ulcers are circular, but large ones are oval and parallel to the long axis of the stomach. On section the ulcer shows diffuse fibrosis of its wall with replacement of the muscularis and fibrosis and thickening of the serosal surface. Partially obliterated blood vessels may be seen. An ulcer of this

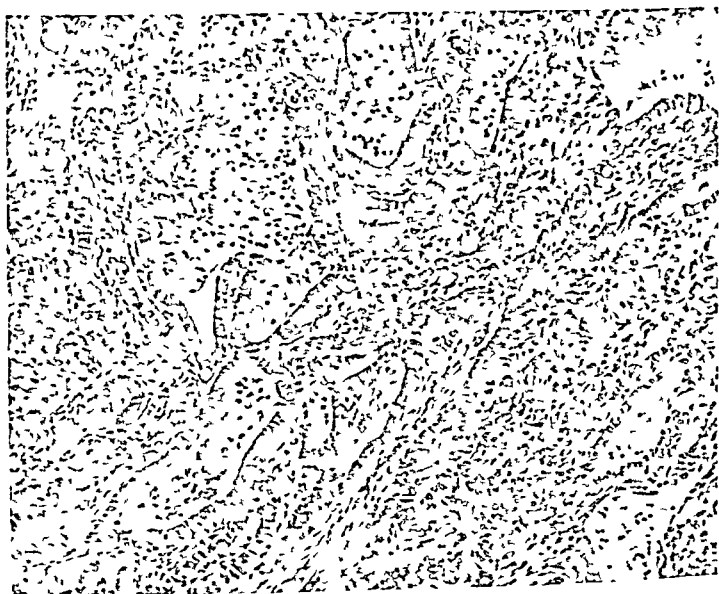


FIG. 368.—Typical fairly well-differentiated adenocarcinoma of the stomach (moderate enlargement)

variety which has recently become carcinomatous seldom shows enough macroscopic changes to justify a definite diagnosis of cancer. At times near the margins of the ulcer there is poorly defined, slightly elevated, submucosal thickening. As the carcinoma grows, it tends to obliterate the old ulcer, but replacement of the base of the ulcer is delayed until the last. Stoerk believes that radiating gastric folds extending around a carcinoma are evidence of a pre-existing benign ulcer (Fig. 383).

The histologic criteria for making a diagnosis of carcinoma arising on the basis of a pre-existing chronic ulceration are as follows. The base of the ulcer is devoid of carcinoma and there is invariably destruction of the muscularis with replacement by dense fibrous tissue. The ulcer floor is made up of

quently presents a slight nodulation. The pyloric ring muscles frequently show hypertrophy (Fig 366). The muscularis is not involved (Gutmann). It shows multiple microscopic areas of change in the overlying epithelium with disturbances of architecture and replacement by the glandular type of carcinoma. At times there is normal epithelium between the areas of disease which, as Mallory indicated, may have multiple foci of origin.

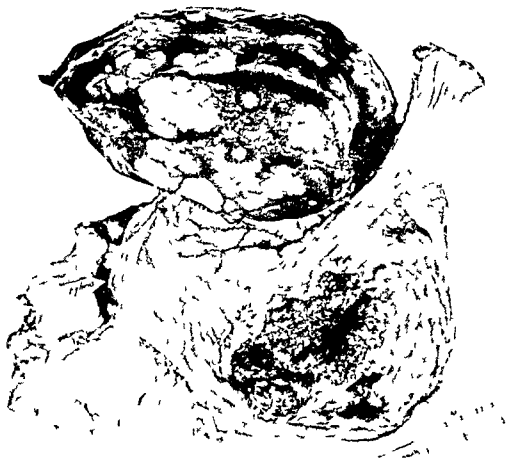


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sect and granulation tissue. The free ends of the muscle are bent upward and the ulcer margin ends are sharply demarcated against the connective tissue of the base (Kerr 1938). Often there is fibrous thickening on the serosal surface which is continuous with the base of the ulcer. Small arterioles are often overreacted. These signs indicate a process of long duration. Carcinoma usually occurs in the margins of the ulcer in single or multiple zones and presents a disorderly glandular pattern. As the disease spreads it extends out to the serosal surface and only in an advanced stage is the base of the

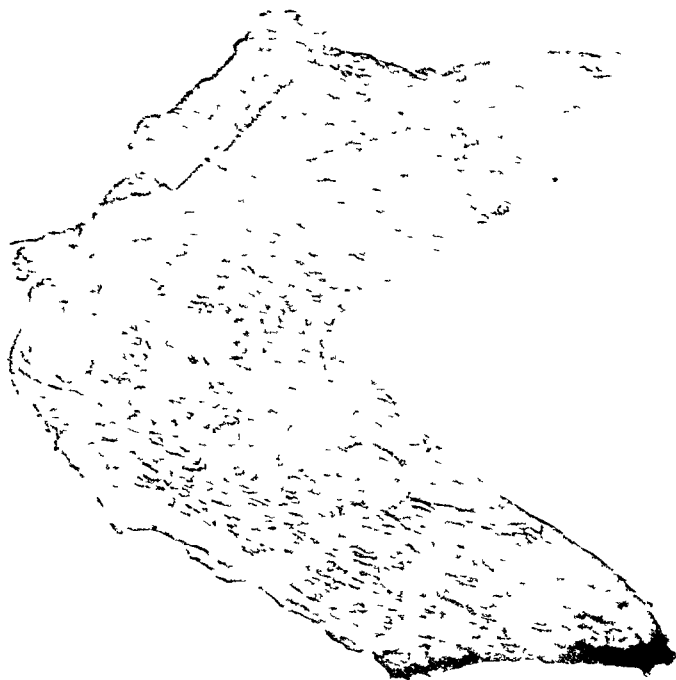


Fig. 372.—Gross specimen of the stomach with two large ulcers of the pyloric antrum. (Courtesy of Dr. A. P. Sisson, Department of Surgical Pathology, Columbia University, New York, N. Y.)

ulcer invaded. Fusion of the muscularis mucosa and muscularis propria is said by Newcomb to occur in 100 per cent of the patients with chronic peptic ulceration. Gomori felt that the presence of this sign depended predominantly upon the stage of the ulceration and found actual fusion in only thirty-four of 64 cases. Carcinoma only rarely occurs on the basis of a healed scar due to pre-existing ulcer.

*Ulcerating Carcinoma*.—The primary ulcerating carcinoma has shallow rather than overhanging edges with fairly extensive and sometimes nodular submucosal infiltration around the borders of the ulcer (Fig. 372). Sections of

Fig 369



Fig 370

Fig 369—Cystic gland occurring in chronic gastritis

Fig 370—Differentiation of the lining epithelium of the stomach to the intestinal type in chronic gastritis

Carcinomas arising from parietal or chief cells are extremely rare. Only nineteen adenocarcinomas of the pyloric area of the stomach have been reported (Wood, 1943). Carcinoid of the stomach (Plaut) and adenomyomas have also been reported (Stewart, 1925).

*Advanced Carcinoma*—Advanced carcinoma unfortunately makes up the greatest proportion of tumors of the stomach. Its frequency is naturally extremely high in post-mortem studies. The tumor is usually very large, replacing wide areas in the stomach, and is often a combination of the fungating and invasive types. Its appearance depends on its mucin production, cellularity, and the connective tissue content.

All carcinomas of the stomach are adenocarcinomas varying only in degree of differentiation from very well-differentiated (Fig. 368) to disorderly, bizarre patterns. If multiple sections are taken, the pattern often varies from section to section. The amount of connective tissue in the tumor will also vary from minimal to extreme desmoplasia. The same may be said of mucin production, which is variable. With mucin stains, however, practically every case will reveal small amounts of mucin in a few cells or perhaps the entire lesion will contain an overwhelming amount of mucus with only a few carcinoma cells floating within it. At times blood vessel invasion may be seen.

The local spread of carcinoma within the stomach is important particularly from the standpoint of treatment and prognosis. The superficial spreading variety may involve wide areas of mucosa and submucosa even up to 54 sq. cm. (Stout). The linitis plastica may also spread to involve large areas by direct invasion. This is manifest by nodular thickening and fixation of the mucosa. In the advanced carcinoma there is usually an extension through the wall of the stomach and there may be variable degrees of esophageal and pyloric obstruction because of this extension (Figs. 379 and 381). In advanced carcinoma, tumor nodules are frequently seen on the serosal surface of the stomach, and it is not infrequent to find direct extension to the liver (Fig. 367), diaphragm, transverse colon, the pancreas, and the hilus of the spleen. It was once thought that carcinoma of the stomach stopped its local spread at the pylorus, but 25 per cent of the surgically resected cases studied by Castleman showed invasion of the duodenum. Tumor can involve any layer of the duodenum with the exception of the mucosa.

Gastritis probably should not be divided into hypertrophic or atrophic varieties but should simply be called *chronic gastritis*. When gastritis is associated with advanced carcinoma it is usually found either surrounding the tumor or as a pangastritis. Gastritis has an inflammatory and an epithelial component. The inflammatory element is made up of an increased number of plasma cells and lymphocytes, with focal accumulations of lymphocytes which at times form germinal follicles. Along with these changes there is interglandular fibrosis. The epithelial changes (most important) are related to dedifferentiation of the specific cells to nonspecific mucous glands and the formation of epithelium resembling that in the large bowel (Fig. 370). Large cystic glands are often present. Stout has never been able to find any direct transition between the atrophic cell of gastritis and the cancer cell.

the ulcer show partial or complete replacement of the muscularis by tumor but there is no fibrosis. As this tumor becomes larger, the ulceration becomes deeper and the submucosal extent becomes greater (Fig 373). Vascular changes are not present. Ulcerating carcinoma shows no microscopic evidence of a previously existing chronic process. The tumor infiltrates all layers of the stomach, tends to spread submucosally, and is present throughout the entire ulcer bed.

*Polypoid Carcinoma*—The polypoid carcinoma may, in some instances, arise on the basis of pre-existing polyps. Pearl divided polyps into two varieties: the congenital neoplastic variety with a definite stalk freely movable on the submucosa with the muscularis mucosa within this stalk and normal mucous membrane between the polyps, and the inflammatory hyperplasias or pseudopolyps which are flatter, do not present a definite stalk, are immovable on the submucosa and have no invagination of the muscularis mucosa. At times early carcinomatous changes may be recognized in a polyp or such an origin may be suggested. As polypoid tumors enlarge and fungate their origin from a pre-existing polyp becomes merely a conjecture. These lesions are well delineated, grow mainly within the lumen of the stomach and may become very large, particularly if they are in areas such as the cardia where obstruction can only occur late (Fig 375).

*Polypoid Carcinoma With Moderate Invasion*—This tumor is merely a more advanced stage of the polypoid variety combined with invasive characteristics. Its margins are not sharply defined and the degree of invasion and replacement of contiguous stomach wall is variable.

*Limitis Plastica*—This is a rare variant of carcinoma which, because of its rarity and its somewhat bizarre nature, has been the subject of profuse writing and frequent illustrations far beyond its merit. Stomachs affected by these tumors are often referred to as the leather bottle type because of shrinkage of the organ. In an advanced stage the wall of the stomach is markedly thickened and on its serosal surface fibrous nodules may be seen. A cross section of the stomach reveals considerable hypertrophy of the muscularis which is particularly prominent in the pyloric area (Fig 377). Bands of fibrous tissue can be seen coursing through the wall of the stomach which is rigid with a cartilaginous consistency and the submucosa is thickened. Fairly frequently there is an associated ulcer in the pyloric region. The mucosa is invariably firmly fixed to the submucosa and later, in the more advanced stages, to the muscularis (Saphir).

Microscopically there may be a great deal of difficulty in diagnosing a limitis plastica because of the overproduction of connective tissue. This fibrosis is hyaline in some areas and is accompanied by large numbers of inflammatory cells, particularly plasma cells and mononuclears. The fibrosis extends not only to the submucosa, but replaces areas of muscularis and is present on the serosal surface. There is hypertrophy of the muscularis, and areas of superficial ulceration may be present. Because of the inflammation and fibrosis and the small number of tumor cells present, this lesion was thought for many years to be only inflammatory (Saphir).

type had 95 per cent. Distant nodes along the aorta, around the head of the pancreas, and above the diaphragm may eventually become implicated in advanced stages. Left supraclavicular lymph nodes are mentioned in every textbook as a common site of metastatic involvement. This finding, however, has been infrequent in our experience, Lange observed 210 cases and found supraclavicular involvement in only nine. In 143 consecutive untreated cases of carcinoma of the stomach which came to autopsy, fifteen (10 per cent) showed no lymph node metastases (Stout). Eleven other cases were limited to the immediate vicinity of the stomach, one had no metastases but had involved the duodenum, ten showed metastases to gastric lymph nodes, and only ten showed metastases to supraclavicular and cervical lymph nodes.

In advanced cases, peritoneal implants and metastases in the region of the rectal shelf appear, and because of fibrous reaction they may constrict and locally invade the outer layers of the rectum, causing partial obstruction. Diffuse lymphangitic metastasis to the lung is not unusual in cancer of the stomach. The frequency of bone involvement is not known inasmuch as post mortem examinations are usually sketchy on this point, but in general the proportion of bone metastases found is small. Liver metastases are frequent. Metastases to the ovaries are relatively rare (less than 5 per cent). When encountered they are usually bilateral, causing moderate enlargement of these organs.

In Stout's post-mortem series, metastases were present in the liver in 70 per cent, peritoneum, omentum, and mesentery in 43 per cent, lungs and pleura in 33 per cent, and bones in 11 per cent.

*Lymphosarcoma* very commonly involves the perigastric and adjacent retroperitoneal lymph nodes, and metastases to spleen, pancreas, and liver are common. Generalized spread occurs late in the disease. *Leiomyosarcomas* may metastasize to regional lymph nodes and frequently to lungs, liver, and other distant organs.

### Clinical Evolution

*Nonpainful Gastrointestinal Symptoms*—In the majority of instances the patient with carcinoma of the stomach notices a vague epigastric uneasiness after meals with moderate distention and a sense of heaviness in the epigastrium. Most patients give no history of previous gastrointestinal disturbances. The indefinite symptoms may be accompanied by relatively easy physical and mental fatigue, and an inexplicable distaste for food, particularly meat. With the continuation of the symptoms, a slow but progressive weight loss may ensue, accompanied by a minimal degree of secondary anemia. Unfortunately, during this period the diagnosis of cancer of the stomach is seldom considered, the patient is classed as neurotic, given symptomatic medication for the anorexia, and treated for the anemia without resort to diagnostic roentgenology. As the disease progresses, the diagnosis is clarified by symptoms due to pyloric obstruction, extreme weight loss, or some other easily recognizable clinical finding.

*Ulcer Variety (Painful)*—This clinical type is much less frequent. Sometimes there are periods of remission lasting a number of years. These are

*Lymphosarcoma* of the stomach has three gross variants the most common forms a large, lobulated soft tumor mass growing within the lumen of the stomach (Fig 371), the second forms disclike areas, and the third shows diffuse involvement with giant rugae resembling cerebral convolutions. These tumors gradually increase in size, invade the muscularis, form a subserosal tumor, infrequently obstruct the lumen with polypoid masses, and occasionally form diffuse thickenings of the stomach wall. They most often involve the curvatures of the stomach. Of seventy-four cases in which there were available data (Taylor), there was involvement of one or both curvatures in fifty-five, diffuse involvement in ten, and pyloric stenosis in only six. As the process continues, these ulcers may ulcerate and show areas of necrosis and zones of hemorrhage. *Lymphosarcoma* of the stomach may be a secondary lesion (Buschke). Its microscopic appearance does not differ from lymphosarcomas elsewhere.

In the mesodermal group of benign tumors the most common is the *leiomyoma*. These tumors, for the most part, grow in the wall of the stomach and rather infrequently involve the pyloric area. Benign tumors are often multiple. The majority are within 4 cm. of the cardioesophageal junction and more frequently within closer proximity to the lesser curvature than the greater curvature. They arise from the internal and external musculature (Rieniets). They are submucous, intramural or subserous. If they grow toward the stomach, ulceration combined with surrounding gastritis occurs. These tumors are usually well delimited, fairly homogeneous and firm and on section may show areas of hemorrhage. Microscopically they are usually cellular and tend to show a rather homogeneous picture. Mitotic figures are rather few in number. *Neurofibromas* have very much the same gross characteristics as the leiomyomas. What percentage of these cases become sarcomas is unknown. It may be extremely difficult to determine whether some particular tumor is benign or malignant.

**METASTATIC SPREAD**—By way of the lymphatics cancer of the stomach may extend into the muscularis and go directly to the serosal surface or ascend or descend within the muscular layers and take exit at levels above or below the primary lesion. The location of the tumor to some extent determines the regional nodes which will be involved. It is particularly common for nodes in the region of the left gastric vessels to be implicated, and eventually nodes around the celiac plexus are heavily infiltrated.

In surgical specimens the proportion of node metastases is naturally related to the type of tumor and the carefulness with which the regional nodes are examined. Coller (1941) demonstrated by his clearing methods of surgical specimens that there were lymph node metastases in 75 per cent of his patients. He also established that there was no correlation between the size of the node and its chance of containing tumor for in the majority of instances even when there was no gross evidence of metastases disease was found microscopically. The most important lymph node metastases found by Coller were in the inferior gastric subpyloric and superior gastric areas. He then stressed the fact that the polypoid neoplasms had only 60 per cent metastases while the sessile

### Diagnosis

The detection of early carcinoma of the stomach by radioscopic examination of asymptomatic individuals has met with discouraging results. According to Levin one can expect to find approximately 1 case of carcinoma of the gastrointestinal tract for every 1 000 individuals examined at the age of 65 years.

FIG. 372

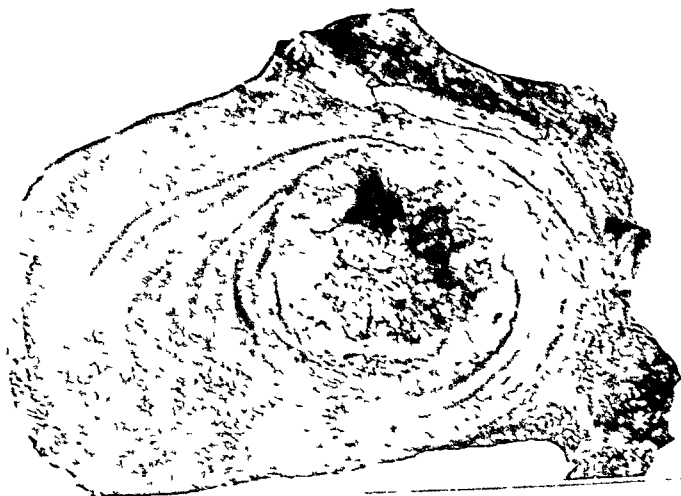


FIG. 373

FIG. 372.—Primary ulcerating carcinoma fairly well delimited with nodular infiltration around the periphery.

FIG. 373.—Cross section of the ulcerating carcinoma of FIG. 372 showing invasion of the entire wall of the stomach by grayish-white tumor.

St John and Swenson (1944) reported a series of 2 432 individuals over the age of 50 years with no digestive symptoms in whom three unsuspected malignant gastric tumors were found: two carcinomas and one lymphosarcoma. But

periodic and relieved by alkaline powders, food or other symptomatic remedies. Pain occurs shortly after eating and may be relatively severe but the character of this pain may change to become more persistent, oppressive, and associated with weight loss. A diagnosis of peptic or duodenal ulcer may be made and an ulcer regime prescribed. In a high percentage of instances this procedure engenders considerable clinical improvement. It is not unusual for the patient to gain weight, and, if iron is given, for the anemia to respond to it. But if the symptoms are caused by carcinoma, after a variable period of time they will recur with increased vigor. If carcinoma of the stomach perforates it suggests a perforated peptic ulcer in approximately two-thirds of the instances (Aird).

**Occult Carcinoma**—Unfortunately in a number of instances carcinoma of the stomach may give no complaints leading to an early diagnosis. The patient may not present weight loss or pain and the first symptoms are due to metastatic disease. This may be manifested by an enlargement of the abdomen due to a nodular liver or the presence of fluid. Rarely dyspnea will ensue due to lymphangitic lung metastases. In other instances jaundice or anemia or a supraclavicular metastasis develops.

Whatever their clinical type of onset carcinomas of the stomach resemble each other in their terminal stages. The patients lose a great deal of weight and may develop considerable pain and symptoms and signs of obstruction may occur due to the tumor occluding the esophagus or pylorus which in itself, may cause death. Without obstruction bleeding from a large ulcerating lesion occurs and obstinate progressive severe anemia with palpitation and weakness is apparent. Or ascites occurs and in a few instances the tumor may metastasize to lymph nodes around the bile ducts and cause a terminal jaundice. In relatively rare instances the tumor may perforate and a terminal peritonitis follow. Often bronchopneumonia is the immediate cause of death. In a series of post mortem cases studied by Stout twenty six (18 per cent) of the patients died while the carcinomas were still theoretically operable.

**Lymphosarcoma** of the stomach may be very slow or rapid in evolution. The patients with lymphosarcoma of the stomach very frequently have pain of the ulcer type. Dyspepsia, anorexia and weight loss are common. It is interesting that *obstructive phenomena in lymphosarcoma of the stomach are infrequent*. As the disease progresses secondary clinical signs such as weakness and profound weight loss appear. Bleeding into the gastrointestinal tract and persistent diarrhea are common. Massive hemorrhage can occur. The patients usually die from generalization of the process.

**Benign tumors** remain dormant for an unknown period of time. Most of them never cause any symptoms and are found only incidentally at autopsy. A few of them however, because of increased growth may cause gastric symptoms and if the mucosa is eroded may result in sudden profound gastric hemorrhage. This hemorrhage is particularly frequent in the ulcerating leiomyomas. In the presence of associated gastritis anorexia may appear with weight loss. The patients with benign tumors seldom die except from severe hemorrhage. If one of the mesenchymal tumors becomes malignant hemorrhage or distant spread of the disease can take place.



patient, usually a male with marked loss of weight, a large palpable mass, and with ascites, is familiar. In a few instances the clinical signs and symptoms of metastases will be noticed first.

On inspection of a patient with early carcinoma of the stomach, nothing is usually observed. However, if obstruction exists, there may be evidence of weight loss and in certain instances the mucous membranes may appear pale.



Fig. 375.—Polypoid well-circumscribed carcinoma of the stomach.

due to anemia. The patient should be carefully scrutinized for presence of mild jaundice. If this is present, it very frequently means obstruction of the biliary tree due to metastatic lymph nodes. At times the falciform ligament is involved by tumor, which spreads down to implicate the umbilicus. Peristaltic waves going from left to right may be seen in early obstruction. If the lesion is in the region of the pylorus and the patient has lost any considerable amount of weight, a large dilated stomach can easily be visualized. The supra-

the prolonged radioscopic examination of such a large number of individuals to find such a few early lesions renders prohibitive this attack of the problem. Patients with atrophic gastritis, pernicious anemia, achlorhydria or ulcers of the stomach should have periodic gastric examinations by competent roentgenologists (Rigler). These examinations should be combined with gastroscopy if possible.



Fig. 344—Roentgenogram of ulcerating carcinoma shown in Figs. 337 and 338.

It is of paramount importance that the clinician should direct his efforts to diagnose carcinoma of the stomach when the symptomatology is still uncertain and the diagnosis is difficult. Patients over 40 years of age with mild anorexia, dyspepsia, slow digestion, or asthenia should be suspected of having carcinoma of the stomach. If the patient has no previous history of ulcer and suddenly develops symptoms suggesting ulcer, this also may be suspicious. The diagnosis depends on two things alone: first, carcinoma must be suspected by the clinician; and second, the patient must be referred to a competent roentgenologist. Some cases may be diagnosed at a fairly early stage because of symptoms of esophageal or pyloric obstruction. The diagnosis of advanced carcinoma of the stomach can be made at a glance. The emaciated, elderly

nation. But in the majority of cases a clinical, radiographic, or pathologic diagnosis is made without difficulty.

Stout mentions that hematemesis in a young person without evidence of obstruction is a significant sign of *lymphosarcoma*. Melena is rather frequent and occult blood is invariably present in the stools. Rather infrequently lymphosarcoma of the stomach may perforate, causing an acute abdominal syndrome (Koucky).

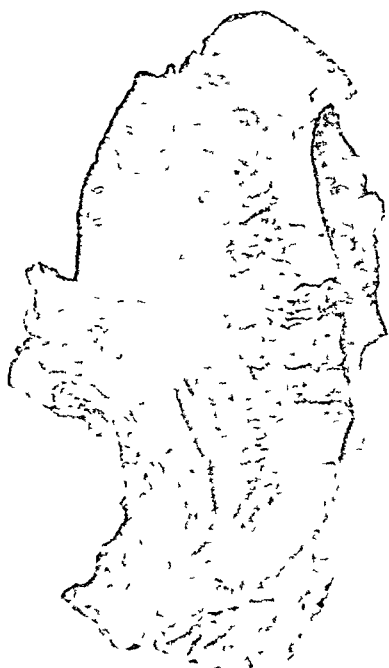


Fig. 377.—Gross specimen of carcinoma of the stomach, linitis plastica type. Note small size of the stomach and hypertrophy of the muscularis.

**Roentgenologic Examination**—The roentgenologic study is the most important single examination in the diagnosis of carcinoma of the stomach. It should be emphasized that it may be necessary in the early cases to make repeated studies. The procedure in the hands of a competent roentgenologist demonstrates malignant disease if present in 95 per cent of the instances. It is unfortunate, therefore, that this examination is so often delayed until after the disease has become so advanced that its presence is obvious. The study should be made when the clinical history and examination are equivocal and when carcinoma of the stomach is only a suspicion rather than a very strong probability.

Radioscopy is a much more important procedure than radiography in the diagnosis of carcinoma of the stomach, for the observation of the dynamics of

clavicular and axillary regions should be palpated in search of enlarged lymph nodes. At times a firm, nonpainful mass may be felt within the abdomen. It is not rare to find also a large nodular liver. A rectal palpation is imperative, for if a rectal shelf is found this means advanced disease. A rectal shelf is due to peritoneal metastases in the cul de sac. These metastases produce some connective tissue and form a mass. This is felt on rectal examination as a poorly defined extramucosal constricting nodular mass. It is usually associated with ascites.



Fig. 37C—Roentgenogram of case illustrated in Fig. 3A.

If the tumor is not advanced and no mass is present a definite diagnosis can only be made roentgenologically. In a few cases in spite of complete clinical, radioscopic, and laboratory information exploration is necessary to determine the nature of the process. In an even smaller number, a definite diagnosis is not made until the specimen has had a complete pathologic exami-

delay in clearance, and mucosal deformity. The stomach usually reveals a deformity which may be unilateral or circumferential, and the filling defect is best visualized in the air-filled cardia. If too much barium is used, however, this filling defect may be obscured. The mucosa frequently shows obliteration or irregularity, and the cardia is often contracted and deformed. There may also be an increased distance between the cardia and the diaphragm. The gastric lumen is often narrowed at the site of the lesion. A thick mixture of barium is of great value in observing the esophagocardiac junction, but if too much barium is used the filling defect may be obscured.



Fig. 379—Advanced carcinoma of the stomach. Note widespread involvement of the stomach with invasion of the walls and extension to the serosal surface.

The roentgenologic diagnosis of advanced carcinoma is relatively easy, for often a palpable mass is felt and fluoroscopy shows an extensive lesion with ragged defects situated in the outline of the stomach wall. There are large areas of ulceration, delay in emptying time, and perhaps an extragastric mass (Fig. 380). The leather-bottle shape of the stomach in *limitis plastica* is typical (Fig. 378).

the stomach is vital. The difficulties of recognition occur particularly in early carcinoma, in the presence of obstructive lesions, and in small carcinomas involving the cardia. The early changes may be limited to the mucosal patterns which can best be observed with the use of radioscopy. Spot film devices are helpful in recording these early lesions. The roentgenologic recognition of the superficial carcinoma of the stomach has been extensively described by Gutmann. This lesion, invariably limited to the mucosa and submucosa, occurs in the pyloric region and is often accompanied by superficial areas of ulceration.



Fig. 318.—Roentgenogram of carcinoma of the stomach. Ulceris plastica type with leather bottle shape deformity and prepyloric ulceration.

Because of its superficiality, it is often missed by conventional roentgenographic studies and cannot be disclosed except by good radioscopic technique where it is seen as a persistent defect with rigidity of a small area of the stomach wall. This rigidity is enhanced by spasm of the stomach muscle in the immediate neighborhood of the lesion. This superficial filling defect persists regardless of therapy. It must be emphasized that the roentgenologist is the only person who can make an early diagnosis of this lesion.

The diagnosis of carcinoma of the cardia is very often difficult, for the lesion usually cannot be palpated. The changes are often present both in the esophagus and in the stomach (Fig. 362). The esophagus may show dilatation



FIG. 51.—Carcinoma of the cardia with secondary invasion of the esophagus.

The roentgenologic differentiation between benign and malignant *gastric ulcers* is based on innumerable factors. The benign ulcer is located on the lesser curvature in approximately 80 per cent of the instances, in the pylorus in 10 per cent and in the cardia or remaining portion of the stomach in 10 per cent. The relative probability that ulcers found in different areas of the stomach are carcinomatous is illustrated in Fig. 387. The prepyloric area is an extremely common site for the development of carcinoma and if an ulcer is present in this region it has a 65 per cent chance of being due to carcinoma. This area



Fig. 380—Extensive irregular filling defect of the prepyloric region (same case as illustrated in Fig. 379)

excludes the pyloric ring and according to Hampton the ulcer must have its center no more than 2.5 cm. from the ring. If the ulcer occurs on the greater curvature it has an almost certain chance of being malignant, but only a very small percentage of all carcinomas occur in this area. Matthews (1935) collected only twenty-four benign ulcers of the greater curvature in the medical literature. If an ulcer crater is located beneath the level of the lesser curvature with a zone of tumefaction with halolike margins surrounding it, this almost without exception signifies carcinoma (Carman). Benign and malig



nant ulcers alike may be smooth or only very slightly irregular. A markedly irregular or ragged crater invariably denotes cancer (Palmer). These benign ulcers are *extramural* in contrast to the intramural character of the malignant ulcers (Figs. 384 and 385). They do not present a palpable mass and their margins are well defined, smooth, and rounded, often with exaggerated rugae. Tenderness is commonly present, and the tone and peristalsis are increased. The rugal patterns often converge into the ulcer crater in contrast to their effacement in cancer.



FIG. 383.—Chronic gastric ulcer with convergence of the folds into the bed of the ulcer.

Under medical treatment the acute and subacute benign ulcers usually completely disappear. Chronic benign ulcers, however, particularly the large ones, cannot completely disappear because of replacement or fibrosis of the muscularis which is never renewed by normal tissue. A malignant ulcer by contrast may be smaller, but there is always some persisting defect which may enlarge, even when symptoms improve. The ulcer crater itself may be partially filled by the growth of tumor over the bed of the ulcer. Gutmann believes that in every four cases of a filling defect which fails to heal, there are two benign ulcers, one benign ulcer which has been transformed into a cancer, and one carcinoma which is primarily ulcerating.



Fig 38 —Carcinoma of the cardia with roentgenologic defects in both the esophagus and stomach

modies. At some time during the examination, the peristaltic waves may pass through the area of apparent rigidity. The clinical history may help to substantiate this diagnosis, and gastroscopy is often diagnostic.

Taylor lists several roentgenologic findings which may suggest the diagnosis of lymphosarcoma. If there are two or more defects in separate portions of the stomach and polyposis can be ruled out, or if there is a large palpable tumor and the pylorus is dilated rather than constricted, the findings suggest lymphosarcoma. Also, lymphosarcoma often presents giant rugae, and the

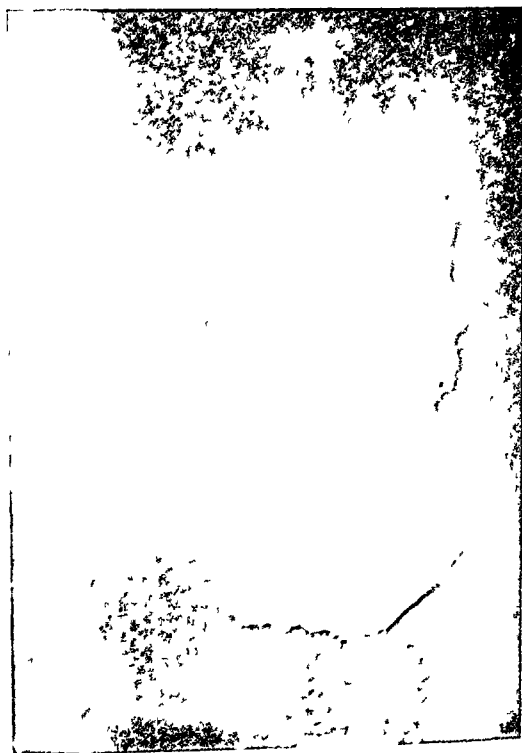


Fig. 5. Characteristic extramural filling defect of the lower curvature due to benign ulcer.

filling defect which they produce is usually associated with phlebotomy. If the curvature of the stomach are the most frequent site of involvement. For emphasis, that changes in peristalsis are probably due to muscular infiltration and that because the tumor grows in the submucosa and therefore remains intact, the tumor may show a large filling defect with irregular margins. If a large lobulated tumor without evidence of obstruction in a young adult, particularly a male in good general condition, there is a possibility that this may be lymphosarcoma.

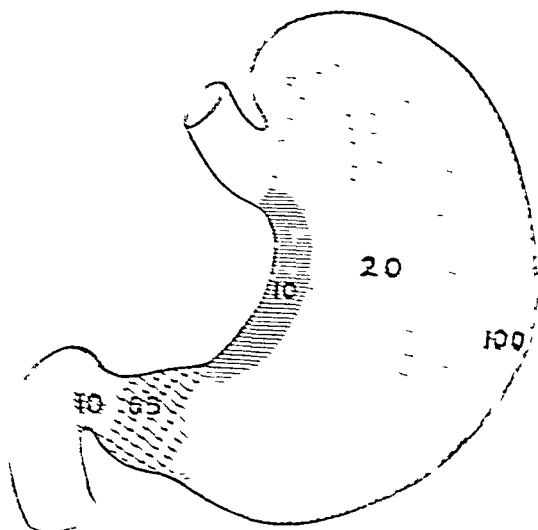
It used to be thought that if an ulcer measured 2.5 cm. or more, the chances were extremely high that it represented carcinoma. The size of the ulcer is not diagnostic. While it is true that the majority of ulcers over 2.5 cm. are malignant, we have seen benign ulcers measuring 9 cm. in diameter and ulcers smaller than 1 cm. which were malignant. In 869 chronic ulcers 2.5 cm. in diameter or less studied at the Mayo Clinic, fourteen were carcinomas (Walters). The average diameter of a series of malignant ulcers reported by Allen (1915) was 2.3 cm. but the average diameter for the benign gastric ulcer was 1.5 centimeters.



FIG. 81.—Characteristic extramural filling defect of a chronic gastric ulcer of the lesser curvature (Same case as illustrated in Fig. 353)

If roentgenologic examination reveals the concomitant presence of a duodenal and gastric ulcer, the chances are high that they are both benign. In a series of over 200 large gastric ulcers observed by Steigmann 19 per cent presented also an active ulcer of the duodenum. If duodenal ulcer is found to coexist with carcinoma of the stomach the ulcer is almost invariably inactive (Fischer).

In *chronic gastritis* there may be intermittent spasms which produce filling defects. These lesions may be easily mistaken for carcinoma unless frequent radioscopy examinations are made perhaps after administration of antispas-



The diagnosis of *benign tumors* of the stomach is often not too difficult. Leiomyomas make up approximately 60 per cent of benign tumors and polyps 35 per cent and the other 5 per cent are rare lesions such as hemangiomas, neurofibromas, and submucous lipomas. More than one half of the leiomyomas are found on the posterior surface of the corpus and the lesser and greater curvatures are free. It is common to have central ulceration. Polyps are usually small and at times multiple, and about three fourths of them are located in the pyloric end of the stomach and may naturally prolapse into the duodenum.

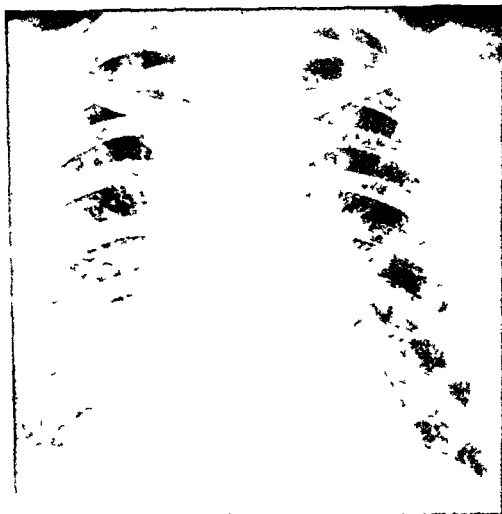


Fig. 356—Lymphangitic metastases from carcinoma of the stomach. Note radiating bands extending out from the hilum to the periphery and prominent mediastinal shadows due to imbedded lymph nodes.

The margins of benign tumors are well defined unless complicated by gastritis. The mucosa is usually normal but may occasionally be hypertrophic. There is no alteration in tone or peristalsis and motility is undisturbed unless the lesion is in the pyloric area. The stomach is freely movable and there is usually no palpable mass except with large leiomyomas.

*Metastases to the stomach* from primary lesions elsewhere are extremely rare but when present most commonly lie within the submucosa in the cardiac

the stomach could be diagnosed by noting extensive peritoneal implants or liver metastases. These findings would considerably shorten hospitalization and minimize the number of exploratory laparotomies. Apparently movable and resectable stomach lesions often show large masses of involved lymph nodes around the celiac axis which cannot be observed by peritoneoscopy. If peritoneoscopy reveals positive findings, it is of definite value, but when it does not, it cannot supplant exploratory laparotomy.

**Laboratory Examination**—Patients with or suspected of having a gastric lesion should have multiple stool examinations, for practically all carcinomas of the stomach show persistent 4 plus *occult blood*. Benign gastric ulcers commonly have occult blood before treatment, but the blood disappears after treatment, while malignant gastric ulcers usually continue to bleed in spite of treatment. Exceptions to both rules have been noted, however. This test, while of value in confirming and explaining the cause of anemia, is not of differential diagnostic value. Bleeding from a lymphosarcoma is quite common.

**Gastric Analysis**—Gastric analysis is another test which should be done routinely in any suspected carcinoma of the stomach, but it is not diagnostic. Achlorhydria or extreme hypochlorhydria is present in about 70 per cent of the patients with carcinoma of the stomach (Huist). Comfort reviewed 79 cases which had had gastric secretory study before the development of cancer of the stomach and noted that this secretory activity was below normal. After an average period of six years, the percentage of achlorhydria had increased from 38 to 64 per cent. Those cases which retained free acidity showed little change. Vanzant showed that achlorhydria increases with age in normal men and women and that about 26 per cent at the age of 70 years have achlorhydria. In men between 20 and 40 years of age, the mean free acidity is about 47 units but decreases to 33 at the age of 70 years. It is interesting that the mean free acidity of women remains very constant at about 33 units in all ages.

Free hydrochloric acid is absent in about 70 per cent of the patients with advanced carcinoma of the stomach. However, in early carcinoma of the stomach, where a diagnostic test is of utmost importance, the gastric analysis is often of no value. This is particularly true when cancer is engrafted upon a previously existing ulcer, for there may be a normal or even elevated amount of hydrochloric acid. In a study of patients with carcinoma of the stomach, Comfort found that where the symptoms had suggested ulcer, the incidence of achlorhydria and the range of free acidity were practically normal for that age, while in the group without symptoms of ulcer the incidence of achlorhydria was apparently four times greater than normal. In a patient with gastric ulcer with no free hydrochloric acid, there is an increased chance that the lesion is carcinomatous. If, however, the hydrochloric acid is normal or depressed, no conclusions can be drawn. Keefer felt that if there was a low secretory volume with complete anacidity, it was almost diagnostic of organic disease of the stomach. There is undoubtedly some relation between acidity and gastritis, for if gastritis is treated symptomatically, the acidity level rises. In multiple gastric polyposis free hydrochloric acid is invariably absent (Pearl, 1943). In carcinoma there is rarely complete achylia gastrica such as is al

portion. It is, however, very frequent for direct invasion of the stomach to occur from malignant lesions arising in contiguous organs. Carcinomas of the lower third of the esophagus very commonly invade the stomach, and others from the gall bladder, liver, pancreas, and large bowel can also secondarily invade it. Benign tumors, particularly pancreatic cysts, can displace the stomach and compress it.

**Gastroscopic Examination**—With the advent of the flexible gastroscope, gastroscopic examination of the stomach has become widely used. It should be emphasized that while this examination is technically simple and usually without danger in skillful hands, there are contraindications to the procedure such as esophageal varices and esophageal obstruction and aortic aneurysm (Schindler). While the technical ability to perform this examination is important, it is not nearly so important as the ability to recognize and interpret the various lesions seen. It may take years to obtain such experience.

Comparisons are often made between gastroscopic and roentgenologic examination. Such comparisons are not helpful, for gastroscopy is another examination which supplements roentgenologic study but does not compete with it. It should be emphasized that in considering one or the other of these procedures the quality of results obtained depends greatly on the caliber of the men who do the work. McNeer has stated that at the Memorial Hospital in New York all cases of resectable carcinoma were visualized by the roentgenologist and gastroscopy merely confirmed the presence of the lesion.

The gastroscope is of value in differentiating chronic gastritis from neoplastic lesions of the stomach, particularly when supplemented by roentgen examination. The gastroscope can reveal lesions high on the greater curvature which may be difficult to visualize by roentgen examination. Certain blind areas cannot be seen with clarity by gastroscopic examination, such as the prepyloric area and the upper part of the lesser curvature. The rest of the lesser curvature and the body of the stomach can be viewed clearly. It is impossible to prognosticate operability or establish a prognosis from the observations of cancer through the gastroscope. The gastroscopist is looking at the mucosa and he cannot determine the extent of the involvement of the gastric wall nor the presence of metastases. Schindler believes that he can determine by observation through the gastroscope whether an ulcer is benign or malignant but others disagree with this concept. Gastroscopy has its greatest value in diagnosing chronic gastritis and in clarifying other gastric pathology and, in a few instances, it may discover neoplastic lesions not seen by the roentgenographic examination (Benedict).

The gastroscopic examination of patients with *lymphosarcoma* may reveal hypertrophy of rugal folds and intact, edematous somewhat stiffened mucous membrane. Later in the evolution of the disease a flat ulcerated area may appear (Rafsky). These changes must be differentiated from gastritis with giant rugae (Schindler).

**Peritoneoscopy**—Peritoneoscopy is the endoscopic examination of the peritoneal cavity through a small incision by means of a cystoscope like instrument. It has been proposed as a measure by which advanced carcinomas of



1943) A gastric ulcer should preferably be treated radically rather than by local excision, for in some instances the surgeon, no matter how capable can not tell at operation whether the lesion is benign or malignant. Of 277 lesions originally believed to be benign, thirty-nine (14 per cent) were carcinomatous (Allen, 1941). Conversely, seventeen patients thought to have carcinoma had a benign ulcer. Of sixty-nine patients who had gastric resection for a supposed ulcer, a pathologic diagnosis of cancer was made in thirty (43 per cent). There were 175 patients treated medically under the misapprehension that the ulcer was benign, and thirteen proved eventually to have cancer, an error of 7 per cent. Twenty-three with an apparent benign ulcer were treated by conservative surgery, mostly gastroenterostomy, and four of these died later of cancer (Allen).

TABLE XIV. RESULTS OF MEDICAL TREATMENT OF GASTRIC ULCERS  
(After Judd, E. S., and Priestley, J. T. Surg., Gynec. & Obst., 1943)

TYPE OF RESULT	CASES	PER CENT
Cure	68	46.0
Symptoms disappeared under medical regimen	23	16.0
Gastric ulcer persisted roentgenologically	7	5.0
Surgical treatment	16	11.0
Definite evidence of carcinoma developed	14	10.0
Death from hemorrhage	1	0.7
Deaths from unrelated causes	17	12.0
Total	146	

*Exploration*—The only chance for complete cure of carcinoma of the stomach is surgical resection of the lesion. Exploration should be carried out in every case unless categorical evidence of inoperability is present. The contraindications to exploration follow:

1. Poor general condition of the patient which is not correctable by thorough preoperative preparation.

2. Evidence of metastases: (a) rectal shelf, (b) nodular liver, (c) metastases to lungs, (d) jaundice, (e) lymph node metastases (supraclavicular, inguinal, and axillary).

The metastatic lesions should be proved by biopsy if possible. Lymphangitic metastases can be seen roentgenologically (Fig. 386). The nodular liver can, at times, be aspirated, but if the aspiration is negative peritoneoscopy can, at times, resolve the diagnosis of metastasis. The diagnosis of rectal shelf can be made at clinical examination by feeling a smooth extramucosal constricting lesion with indefinite margins. It is not too rare to have ascites associated with the rectal shelf, which in turn, indicates peritoneal metastases. The presence of tumor cells can often be ascertained by doing a paracentesis, centrifuging the fluid, and making microscopic sections.

The presence of a palpable mass does not contraindicate operation. A palpable mass was present in 28 per cent of Lahey's operable group. The roentgenologist cannot determine with exactitude whether or not any given lesion is operable.

ways found in pernicious anemia. Unfortunately, where the test is most needed as a diagnostic procedure (such as in chronic gastritis, carcinoma, or gastric syphilis), achlorhydria is often found and consequently the test is of no value.

Taylor studied thirty three patients with *lymphosarcoma*, seventeen of whom showed normal or elevated free hydrochloric acid. This is probably explained by the fact that these tumors arise in the submucosa and the function of the mucosa continues for an appreciable time before there is diminution or cessation in the output of hydrochloric acid. Benign tumors of the stomach and leiomyosarcomas usually do not show any specific alteration of their gastric analysis except that free hydrochloric secretion tends to be depressed in the presence of large ulcerating tumors with secondary gastritis.

**Other Laboratory Procedures**—In all patients with carcinoma of the stomach in both pre and postoperative periods chemical and hematologic control by laboratory procedures is of paramount importance. The level of serum proteins should always be investigated for with carcinoma of the stomach there is frequently some degree of hepatic dysfunction which results in depression of the serum, albumin and prothrombin fabrication (Oppenheim). In Ariel's study approximately 60 per cent of the patients had hypoproteinemia and about 70 per cent had anemia. It is essential also that the carbon dioxide combining power, chlorides, nonprotein nitrogen, complete blood counts, and particularly hematocrits be investigated as indicated.

In many instances there is a normochromic anemia, the count often shows elevation rather than depression of the total white cell level, and there is no lymphocytosis. Studies of the bone marrow in patients with gastric cancer show a tendency toward erythropoietic hyperplasia (Cheney), and infrequently a leucemoid reaction may be present (Kugelmeyer).

### Treatment

About 10 per cent of *gastric ulcers* prove postoperatively to contain cancer (Judd, 1943). Errors in diagnosis occur in spite of a complete history, the best roentgenologic and gastroscopic examinations, and thorough laboratory investigations. It is therefore imperative that a fairly definite regime be set up for the care of patients with gastric ulcers. There is no doubt that patients with tumors which appear benign but which are later proved to be malignant receive relief from medical treatment. It is extremely important that there be complete disappearance of the lesion both roentgenologically and gastroscopically before thought of surgery is abandoned, and these patients should be carefully followed for several years. Gutmann emphatically stresses that in every gastric ulcer which is carcinomatous, a defect persists. If there is any question of whether the lesion is benign or malignant or whether the gastric ulcer has penetrated into the muscularis there should be no hesitation in doing a subtotal gastrectomy. The operative mortality in the hands of a competent surgeon ranges between 1 and 3 per cent. In 146 patients with supposedly benign gastric ulcers treated medically and then followed for five to twelve years (Table XIV) cure occurred in only sixty eight (46 per cent) (Judd

more extensive, a total gastric resection can be done, but this, of course, increases the operative mortality. Unfortunately, where a total gastrectomy has been necessary, the lesions were large and far advanced, and probably in many instances there was residual carcinoma. At times the lesions have fixation to other structures. Portions of or entire neighboring organs, including the spleen, pancreas, transverse colon, liver, and diaphragm have been removed by experienced surgeons, but the more radical the procedure, the higher the operative mortality. These extremely extensive operations are rarely justified in view of the results. In practically all instances carcinoma remains in distant lymph node groups. This is in contrast to carcinoma of the large bowel where local extension without distant metastases frequently occurs and extensive operations seem justified.

In 1943, Pack summarized the results of 303 *total gastrectomies*. The mortality was 37 per cent and there were only sixteen patients (5 per cent) who were known to have lived more than three years. It seems logical that this operation should be reserved for smaller rather than larger lesions, for with far-advanced cases the operative mortality is almost prohibitive, and the number surviving five years is too small.

The postoperative care of patients who have had subtotal or total gastric resection is also of extreme importance and will necessitate vigilance. The blood must be maintained at normal levels and particularly the serum proteins kept high because liver function is often poor and fabrication of serum proteins, especially albumin, is inadequate.

*Palliative Surgery*—Although in the past measures to relieve obstruction due to tumor were frequently carried out, the majority opinion today is apparently against such operation. Life is not prolonged and the operative mortality is high. At times gastric resection is found to be palliative rather than curative for the tumor is found to be present right up to the limits of the excision. This type of operation appears to be more logical than short circuiting procedures to relieve obstruction. Operative mortality, however, is rather high but in some instances the palliation received is very worthwhile.

*RADIOTHERAPY*—Considering the very small proportion of patients who eventually benefit by surgical treatment of carcinoma of the stomach, the contributions, no matter how small, of any other form of treatment would be welcome. In 1896 Despeignes applied the roentgen rays to the treatment of cancer of the stomach. He and many others who have succeeded him, in hoping for a curative effect of radiations, have been disappointed. Weiner (1915) published the results of the treatment of over 200 patients with cancer of the stomach by roentgen rays, with some temporary results but no permanent cure. Evans and Leucutia (1923) had a similar experience. Gosset and Regaud (1933) treated thirty-one patients with inoperable carcinomas of the stomach by external application of telecurietherapy. In the majority of cases there was no improvement and in a few there were favorable results, but there was no permanent cure. Radiotherapy, however, may contribute unexpected relief and remissions (Meritt, 1936). Some authors have been led to believe that the failure of external irradiation is due to the inability to administer

When there is no evidence contraindicating exploration, then a rigorous preoperative regime should be started, including frequent gastric lavage, transfusions, high vitamin diet, and the administration of substances to increase the serum protein level. At the time of operation the serum proteins, the total blood count, and the general physical condition of the patient should be as near normal as possible. Continuous spinal anesthesia is preferable. At the time of exploration it may be found that resection is inadvisable because of metastatic nodules in the liver, wide direct extension, or peritoneal implants. However, the commonest cause for inability to resect is metastases to inoperable nodes most frequently found in the region around the celiac axis. Biopsy and frozen section of questionably implicated nodes can be made at the time of exploration.

If carcinoma of the stomach perforates, the lesion may be simply sutured and appropriate surgery can be done later on after proper preoperative care. On the contrary, Disgrud recommended that resection of the tumor be carried out at the time of the primary operation. He reported that there was a mortality of 80 per cent in the patients in whom simple closure of perforations was done, probably related to the fact that this procedure involved suturing of carcinomatous tissue with subsequent leakage and peritonitis. McNerly feels that it is wise to biopsy all apparently benign perforating gastric ulcers, for certainly in a number of instances the pathologic diagnosis of carcinoma will be made unexpectedly. About half of these cases are resectable. At operation the etiology of the perforation is not recognized but frozen section can resolve this difficulty.

If a benign tumor of the stomach is present it should be fairly radically resected, for it is practically impossible to tell from the roentgenologic or gross examination whether any given benign tumor is malignant. A fairly high percentage of the leiomyomas are malignant when discovered clinically.

**Gastric Resection**—The resection rate for carcinoma of the stomach has greatly increased in most clinics and the operative mortality has decreased. Gastric resection should be radical because tumor may be cut across along the lesser curvature even though it is not clinically palpable. For instance in thirteen of 53 cases Collier (1941) reported incomplete excision. It has also been shown that when the tumor is located fairly close to the pylorus involvement of the duodenum can be expected and consequently at least the first 3 cm. of the duodenum should also be included in the resection (Castleman). At the time of the removal of the stomach node groups particularly those in the region of the left gastric vessels should also be resected.

If the tumor is located near the cardia then it may be necessary to do an esophagogastric resection for a variable degree of extension along the esophagus may be present. This operation is logical because it can include lymph node metastases as well as extension of the tumor above the diaphragm. Sweet does a transthoracic gastrectomy and esophagectomy for carcinoma high on the lesser curvature, cardia and fundus of the stomach. He reported forty-five cases with partial gastrectomy, esophagectomy and esophagogastric anastomosis with an operative mortality of only 15 per cent. If the tumor is still

Advances have been made in the technical procedure, new drugs are at hand, and pre- and postoperative care have increasingly improved with a resultant fall in postoperative mortality. Table XVI illustrates the differences in the cases seen between 1908 and 1937 and between 1938 and 1942 at the Presbyterian Hospital of New York.

TABLE XV. GROSS ANALYSIS OF CASES SEEN AT MAYO CLINIC BETWEEN 1907 AND 1938  
(NOTE: NUMBER OF FIVE YEAR SURVIVALS, 16 PER CENT OF TOTAL NUMBER SEEN)  
(From Walters, W., Gray, H. K., and Priestley, J. T. Carcinoma and Other Malignant Lesions of the Stomach, 1912, W. B. Saunders Co.)

	NUMBER OF CASES	PERCENTAGE
Inoperable	1,618	43
Exploration only	2,431	22
Palliative procedure	1,039	10
Resection	2,772	25
Total	10,890	100
Survived operation	2,322	84
Operative mortality	450	16
Five year survival	672	24

TABLE XVI. ALLOCATION OF RECENT PROGRESS IN SURGICAL TREATMENT OF CARCINOMA OF STOMACH (NOTE: INCREASED RESECTION RATE AND DECREASED OPERATIVE MORTALITY)  
(From St. John, F. B., and Harvey, H. D. Cancer Teaching Day, 1944)

	NUMBER OF PATIENTS	
	1908-1937	1938-1942
Admissions	960	244
Palliative operations	471	95
Resections	142	89
Resection rate (per cent)	14.8	36.5
Resection operative mortality (per cent)	33.8	17.9

Anschutz, in 1936, reported that in 190 cases the average duration of life after *gastroenterostomy* was only six months. Furthermore, there is little difference in the length of life between those who have *gastroenterostomy* and those who do not.

Subtotal gastric resections for carcinoma have been known to show that tumor was cut across, making the resection palliative rather than curative. Anschutz found that with *palliative resection* 50 per cent of the patients survived a year, 30 per cent two years, and 20 per cent three years.

Carcinoma of the cardia treated by esophagogastric resection is only possible in a limited number of cases. Garlock explored twenty-five of these lesions and was able to resect only nine. There were four postoperative deaths and four patients surviving from seven to eighteen months.

There are various factors which influence the prognosis of therapeutic subtotal gastric resections. All of these are related to the presence or absence of lymph node metastases. In a fairly large series of patients on whom curative gastric resection was done by Anschutz, there was correlation between age and prognosis. Only 5 per cent of the operated patients under the age of 40 years survived five years, in patients between 40 and 60 years the survival was 18 per cent, and in those over 60, it was 28 per cent.

a sufficient depth dose and they have proposed instead the interstitial or intracavitary application of radium as a remedy. In reality these methods of treatment result in a very unequal distribution of radiations and in almost constant untoward effects, without bettering the admittedly poor results of external roentgentherapy. Interstitial and intracavitary irradiation, justified in the early days of radiation therapy (Wielhim), are today veritable therapeutic nihilism (Livingston and Piek). In spite of some radiosensitivity shown by these tumors radiotherapy usually fails because of the pathologic character of gastrointestinal carcinomas in general and because of widespread visceral extension and metastasis particularly prevalent in carcinoma of the stomach. The reasons for the failure are qualitative, not quantitative. The only hope of improvement of results of radiotherapy resides in the conscientious study and application of supervoltage roentgen rays and newly acquired forms of ionizing radiations.

Radiotherapy is quite successful in the treatment of lymphosarcomas of the stomach (Merritt). Usually the diagnosis of lymphosarcoma is not made by roentgenologic observation and often, therefore the stomach is resected because the lesion was thought to be carcinoma. If it is discovered that the primary tumor is a lymphosarcoma and that regional lymph nodes are implicated, it is reasonable to expect that other nodes in that area are also involved and postoperative roentgentherapy should be given. If at exploration the tumor is inoperable and subsequent study of biopsies proves it to be a lymphosarcoma then roentgentherapy should be carried out.

**MEDICAL TREATMENT**—Palliative medical measures should be given for advanced carcinoma of the stomach. Gastric lavage, together with a high protein high vitamin diet, may be helpful, and sometimes small frequent feedings will be of value. The anemia which may accompany even small carcinomas of the stomach may be profound but can profitably be treated with iron (Cheney). Medication to relieve pain should be given as indicated.

### Prognosis

The over all prognosis for carcinoma of the stomach is shockingly poor. By the time the patients are first seen the carcinoma has invariably grown to a large size, has spread to neighboring structures or metastasized distantly and has become inoperable. Many patients die without diagnosis, some reach large general hospitals just before death, and still others who are explored cannot be resected (Fig 389). Oughterson attempts to demonstrate the over all picture of carcinoma of the stomach as seen at New Haven. Noteworthy, the percentage of survivors in the total group makes up no more than 1 or 2 per cent.

The statistics from the urban clinics offer far more optimistic figures. The referring physician naturally submits only those patients on whom resection is conceivable making the percentage resectability much higher (Table XV).

There is no doubt that in areas where cancer education has been wide spread where roentgenologic advances have been made and where physicians are on the alert for the early symptoms there will be a greater number of early cases seen and therefore also a greater percentage of resectable cases.

Advances have been made in the technical procedure, new drugs are at hand and pre- and postoperative care have increasingly improved with a resultant fall in postoperative mortality. Table XVI illustrates the differences in the cases seen between 1905 and 1937 and between 1938 and 1942 at the Presbyterian Hospital of New York.

TABLE XV. GROSS ANALYSIS OF CASES SEEN AT PRESBYTERIAN HOSPITAL, 1907-1919\*  
(NOTE: NUMBER OF FIVE YEAR SURVIVALS 16 PER CENT OF TOTAL NUMBER SEEN)  
\*From William W. Gray, H. K. and Philip J. T. Carpenter and  
Oscar M. Hight, *Journal of the Statistical Society of London*, W. B. Saunders Co.

	NUMBER OF CASES	PERCENTAGE
Resectable	1,648	43
Exploratory	2,471	23
Palliative procedure	1,669	19
Excision	2,772	55
Total	10,560	100
Survived operation	2,222	84
Operative mortality	3,551	16
Five year survival	672	24

TABLE XVI. ANALYSIS OF PRE- AND POST-OPERATIVE SURVIVAL IN THE CASE OF GASTRIC STOMACH (NOTE: 1 CASE OF POST-OPERATIVE DEATH IN 1942 OF 17 MONTHS)  
From St. John F. B. and Patrick H. D. *Cancer Treatment*, Day 1942.

	1905-1937	1938-1942
ANALYSIS	601	244
Palliative operations	371	95
Resections	142	61
Excision rate per cent	14.8	25
Five year survival per cent	8	17.6

Anschutz in 1936 reported that in 190 cases the average duration of life after *gastroenterostomy* was only six months. Furthermore there is little difference in the length of life between those who have *gastroenterostomy* and those who do not.

Subtotal gastric resections for carcinoma have been known to show that tumor was cut across making the resection palliative rather than curative. Anschutz found that with *palliative resection* 50 per cent of the patients survived a year, 30 per cent two years and 20 per cent three years.

Carcinoma of the cardia treated by esophagogastric resection is only possible in a limited number of cases. Garlock explored twenty-five of these lesions and was able to resect only nine. There were four postoperative deaths and four patients surviving from seven to eighteen months.

There are various factors which influence the prognosis of therapeutic subtotal gastric resections. All of these are related to the presence or absence of lymph node metastases. In a fairly large series of patients on whom curative gastric resection was done by Anschutz, there was correlation between age and prognosis. Only 5 per cent of the operated patients under the age of 40 years survived five years, in patients between 40 and 60 years the survival was 18 per cent, and in those over 60, it was 28 per cent.

Undoubtedly, *lymph node metastases* and extension outside the stomach are the most important prognostic factors. In the large series of patients without outside extension or metastases reported by Walters (1941), 45 per cent lived five years. But when metastases were present, the five year survival was only 17 per cent. In the series of 960 patients reported on by St. John, 8 per cent of the 142 in whom resection was done did not have metastases and one half of these survived five years.

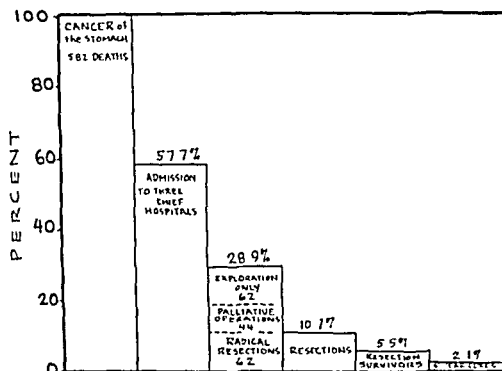


Fig. 252.—Late stage of patients with carcinoma of the stomach. Analysis of a group collected from a large hospital in New Haven between 1931 and 1933. (From Oughterson, A. J. Nat. Cancer Inst., 1941.)

The *type of carcinoma* is also a factor in prognosis, but this again is related to lymph node metastases. The superficial spreading type of carcinoma has an excellent outlook because it so infrequently has involvement of the nodes. In twenty three of the patients reported on by Stout (1945) only 39 per cent had lymph node metastases, compared with 75 per cent in 123 other gastric carcinomas resected during the same period. Stout felt that a 50 per cent five year survival could be anticipated in that group. The five year survival rate in patients with apparently benign ulcers which were later found to be carcinomatous was 40 per cent (Allen, 1945), a good prognosis because of the small percentage of lymph node metastases. Tumors originating in polyps are usually well localized and consequently only rarely have node metastases.

There is a definite relation between *pathologic differentiation* and prognosis. The undifferentiated carcinomas do poorly because of the extremely high incidence of metastases. The linitis plastica type of carcinoma has a short duration and thus an unfavorable outlook (Saphir, 1943). The infiltrating carcinomas as a group also have a high incidence of metastases.



In *extremely radical resections* for very large carcinomas, ultimate salvage is low. For instance, in the 303 total gastrectomies for tumor which Pack summarized, only sixteen of the patients were known to have lived more than three years. Esophagogastric resection done for a limited number of cases of carcinomas of the cardia yields meager results.

In summary, the best results can be given to the well-differentiated, well localized tumor without evidence of lymph node metastases which has had a radical resection.

In Taylor's collected series of 100 patients with *lymphosarcoma* of the stomach, seventy-six had subtotal gastrectomy with a 16 per cent operative mortality, thirteen were living and well five to twenty-two years after the discovery of the lesion, eight were treated by surgery with or without roentgentherapy and five had radiotherapy alone.

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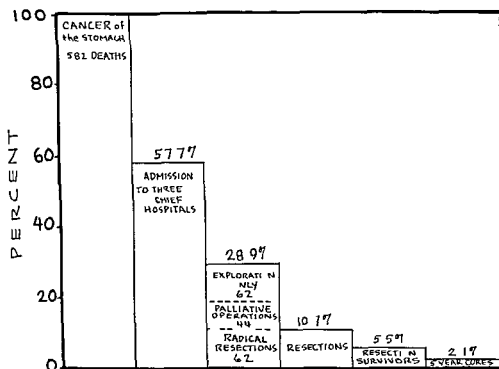


Fig. 389.—Fate of patients with carcinoma of the stomach: analysis of a group collected from metropolitan New Haven between 1931 and 1938. (From Oughterson, A. J. Nat. Cancer Inst. 1941.)

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## TUMORS OF THE SMALL BOWEL

### Anatomy

The small intestine extends from the pyloric ring of the stomach to the ileocecal valve and consists of a small caliber musculomembranous tube divided into three portions the duodenum, the jejunum, and the ileum The limits between the last two portions are arbitrary

The duodenum starts at the pyloric ring of the stomach and follows an upward direction toward the neck of the gall bladder to form its first portion, the duodenal bulb Then it descends as a retroperitoneal structure between the head of the pancreas and the hilus of the right kidney This second descending portion is intimately associated with the head of the pancreas, and into it open the pancreatic and common biliary ducts At the level of the third lumbar vertebra the duodenum bends to form the third horizontal portion which extends to the mesenteric vessels and the fourth portion extends from these vessels to the duodenojejunal angle This sharp bend in the small intestine is situated on the left side of the second lumbar vertebra From there on, the small intestine has a variable length and is divided into loops which occupy mostly the left side of the abdomen and finally open in the large bowel at the level of the ileocecal valve The jejunum is attached to the posterior abdominal wall by the mesentery The mesentery inserts in an oblique line measuring about 12 cm in length and extends from the duodenojejunal angle on the left side of the second lumbar vertebra crosses the midline in a downward direction and ends to the right of the sacrolumbar disc The free border of the mesentery spreads like a fan and measures about 20 feet in length The blood supply of the small intestine comes from the superior mesenteric artery

The mucosal surface of the small intestine is increased by circular folds (valves or Kerl ring) and the villi These folds are of maximum development in the distal half of the duodenum and proximal half of the jejunum They gradually become less prominent in the ileum and disappear at about its mid portion The folds are made up of all layers of the mucosa including muscularis mucosa The villi are formed by mucous membrane and their openings are designated as the crypts of Lieberkuhn The lining epithelium is made up of columnar cells, goblet cells and argentaffine cells Lymphatic tissue is present through the small intestine but becomes most prominent in the ileum where aggregation of follicles is designated as Peyer's patches (thirty to forty in number) The submucosa contains the muscularis mucosa and numerous blood vessels The external and internal layers of the muscular wall are well developed The outer surface is covered by serosa

**Lymphatics**—The lymphatics of the *duodenum* converge behind the head of the pancreas to end in the posterior pancreaticoduodenal lymph nodes. The lymphatics of the *jejunum* and *ileum* run through the mesentery in greater number than the blood vessels and are drained by the mesenteric lymph nodes. Those arising from the terminal segment of the ileum drain into the lymph nodes of the ileocolic chain and at times into a posterior cecal lymph node.

### Incidence and Etiology

Tumors of the small bowel are astonishingly infrequent considering the area of vulnerability. The reported incidence varies, depending on whether the cases are included in a necropsy series or in groups which are recognized clinically. Raiford found that benign tumors of the small bowel were more frequent than the malignant tumors (Table XVII). In his large series malig-

TABLE XVII RATIO OF BENIGN AND MALIGNANT TUMORS OF SMALL INTESTINE  
(From Raiford, T. S., Arch Surg, 1932)

Benign tumors	
Gastrointestinal	210
Small intestine	50 (23.8%)
Malignant tumors	
Gastrointestinal	776
Small intestine	78 (4.9%)

nant neoplasms of the small intestine made up only 5 per cent of the total number of malignant tumors of the gastrointestinal tract.

The reason for the small percentage of carcinomas of the small bowel is as yet unknown. It has been suggested that the fluid content or alkalinity may prevent their growth or that the small number is due to the absence of abrupt bends (such as those in the colon) and because stasis is minimal. It should be emphasized that a number of the malignant tumors, particularly those which arise from smooth muscle and glandular tissue arise from pre-existing benign tumors. Polyposis can occur in the small bowel, and, if present, is a precancerous lesion (Shaw, Cassidy).

### Pathology

**Gross and Microscopic Pathology**—Tumors can arise from any of the tissues normally present within the small bowel but very rarely originate in aberrant pancreatic tissue or within a Meckel's diverticulum (Albright). The classification shown in Table XVIII has proved useful.

The smooth muscle tumor, the *leiomyoma*, is the most common benign tumor of the small intestine—about 80 per cent occur with equal frequency in the jejunum and ileum and the remaining 20 per cent in the duodenum. Rarely the appendix and Meckel's diverticulum may be a primary site (Golden). A small percentage of these tumors arise from the muscularis mucosa but more frequently from the subserosa or from the muscular wall. Those which arise from the muscularis mucosa grow toward the lumen, those from the subserosa grow away from the lumen, and those from the muscularis can grow in either direction. These tumors are of variable size. Those discovered at autopsy as

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## PLATE VI

Lobulated lymphosarcoma of the stomach without pyloric obstruction

Characteristic well delineated leiomyoma of the stomach apparently arising in the submucosa and accompanied by superficial ulceration and chronic gastritis

Fungating circumferential adenocarcinoma of the large bowel

Carcinoma of the rectum with rolled and well delineated edges and almost complete encirclement of the bowel

Untoward effect of irradiations on small bowel with submucous edema and mucosal hemorrhage

Malignant vascular tumor of the small bowel with metastases to regional lymph nodes

TABLE XVIII CLASSIFICATION OF TUMORS OF SMALL BOWEL ACCORDING TO TISSUE OF ORIGIN

TISSUE OF ORIGIN	BENIGN	MALIGNANT
1 Smooth muscle	Leiomyoma	Leiomyosarcoma
2 Glandular epithelium	Adenoma or polyp	Adenocarcinoma
3 Chromaffin cells of the crypts of Lieberkuhn	Carcinoid	Adenocarcinoma (carcinoid)
4 Lymphoid tissue	-----	Lymphosarcoma
5 Fat	Lipoma	Not reported
6 Connective tissue	Fibroma	Fibrosarcoma
7 Nerve sheath	Neurofibroma (also neurilemmoma)	Neurofibrosarcoma
8 Blood vessels	Hemangioma	Hemangioendothelioma
9 Lymph vessels	Lymphangioma	Not reported

incidental findings are usually very small, while those which produce clinical signs and symptoms are much larger, weighing as much as a thousand grams. They are rather firm and if they grow toward the lumen or invaginate from the subserosal area they may finally centrally ulcerate. Grossly it may be impossible to tell whether the lesion is a leiomyoma or a *leiomyosarcoma* unless obvious metastases are present. A fairly high proportion, perhaps half of all the cases are malignant.

Microscopically the leiomyoma is fairly cellular, often with areas of hyaline change, and if the tumor has ulcerated, there is considerable inflammation. Myofibrils may be difficult to identify. At times, because of the bizarre appearance of the cells and the innumerable mitotic figures, a diagnosis of leiomyosarcoma may be made. Unfortunately, some of the tumors which appear benign microscopically may metastasize, while those which appear malignant may remain localized. The leiomyoma in contrast to the tumors of neural origin is nonencapsulated (Stout).

*Polyps* or *adenomas* arising from glandular epithelium may occur anywhere in the small bowel and at times may be multiple. As in polyps of the large bowel, malignant change can take place but the number of *adenocarcinomas* arising from polyps is unknown. Excluding carcinomas arising in the periampullary region of the duodenum, carcinomas in the first and third portions are uncommon. Dixon reported fourteen in the first portion, fifteen in the second, and twenty in the third. The rest of the carcinomas are distributed in about equal frequency in the jejunum and ileum, although in several series jejunal carcinomas are more numerous than the ileal carcinomas. These carcinomas are often constricting, form an annular ring with involvement of the entire lumen of the bowel and completely obstruct the bowel proximal to the lesion (Fig. 390). At times the tumor is *fungating* and *nonobstructing* and shows hypertrophy of its muscularis and considerable dilatation. Microscopically, the benign polyps are similar to polyps found elsewhere and the carcinomas are glandular in nature showing variable degrees of differentiation and often extending through all layers to the serosal surface.

*Carcinoid* tumors can arise in any part of the small bowel but in most instances they appear in the terminal ileum or appendix. These tumors are frequently multiple, often appear to be submucosal and usually present





PLATE VI



Fig. 391 —Photomicrograph of a carcinoid of the ileum. Note restriction of the tumor to the mucosa and submucosa with hypertrophy of the muscularis (very low-power enlargement)

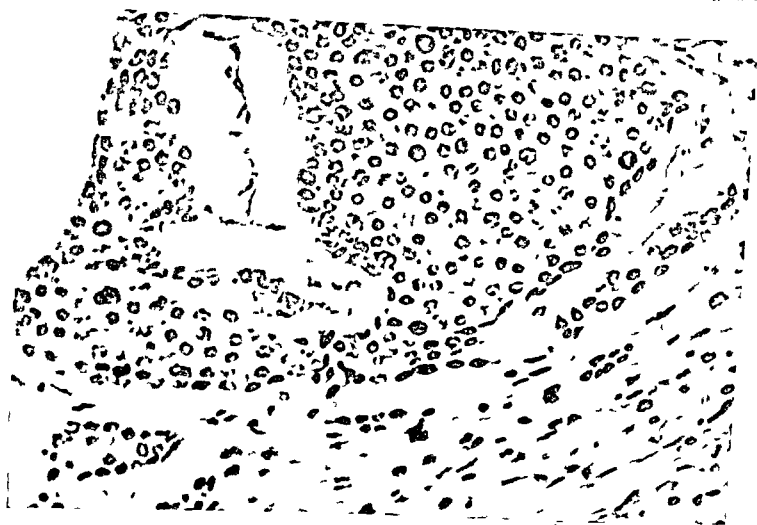


Fig. 392 —Photomicrograph of a typical carcinoid showing uniformity of the cells, fine nucleoli and absence of mitotic figures (high-power enlargement)

only very small areas of superficial ulceration. On section they are orange yellow in color due to the large amount of cholesterol present. This color is present not only in the primary tumor but in the metastases also. A carcinoid tumor may have multiple foci of origin, frequently causes partial obstruction of the bowel, and often invades the entire width of the bowel wall to implicate the serosal surface. With this involvement a bulging of the bowel may result. Along with these changes there is frequently hypertrophy of the muscularis (Fig. 391).



Fig. 390—Adenocarcinoma of the ileum well delineated completely obstructing with metastases to the regional nodes. (Courtesy of Dr. A. I. Stout, Department of Surgical Pathology, Columbia University, New York, N. Y.)

Microscopically carcinoid tumors arise from the chromaffin cells of the crypts of Lieberkuhn. They form well ordered nests with practically no mitotic figures (Fig. 392). All the cells appear similar, they are rather small with fine nucleoli. A variable degree of fibrosis accompanies the tumor and at

submucosa, or giant rugae (Figs 393 and 395). In the terminal ileum, it may rarely intussuscept. So-called round-cell sarcomas of the small intestine are, in all likelihood, true lymphosarcomas (Puente Duany).

The *lipoma* is about the third most common benign tumor of the small bowel. Over one-half of these tumors occur in the small bowel, most frequently (approximately one-third) in the ileum (Schottenfeld). They are often submucosal (about 90 per cent) and form a fairly well-defined tumor mass usually with an intact overlying mucosa. They are occasionally found in the subserosa and may be multiple. They are of variable size and may be pedunculated. On section, lipomas are soft, light yellow in color, and homogeneous. Due to impaired blood supply, necrosis or hemorrhage may occur within them. Microscopically they are composed of normal fat with a variable amount of connective tissue stroma. *Liposarcomas* of the small intestine have not been reported.

The *fibromas*, *neurofibromas*, and *neuilemomas* of the small bowel are relatively few in number as compared with leiomyomas but present very similar gross characteristics. Microscopically the neural tumors are encapsulated (the leiomyomas are nonencapsulated). Fibromas are rare and are made up purely of connective tissue cells. *Fibrosarcomas* and *neurogenic sarcomas* at times occur. *Hemangiomas* are extremely rare and usually single but can be multiple (McClure). They are often submucosal in nature. Microscopically they can be capillary or cavernous. They can invade the muscularis and even perforate retroperitoneally. The malignant variant is extremely rare (Magnusson). *Lymphangiomas* are equally rare, polypoid, soft, and velvety and are made up of small nodules. There may be yellowish zones in the folds of the mucous membrane (Poppel).

**METASTATIC SPREAD**—The leiomyosarcomas grow slowly and develop metastases in the liver, lungs, and peritoneum but infrequently metastasize to the lymph nodes. Generalized metastases have been reported (Pack, 1935, Ghon, 1909). The neurofibrosarcomas and fibrosarcomas metastasize to the same areas.

Adenocarcinomas metastasize first to the regional lymph nodes and sometimes to liver, lungs, and bone. A variable percentage of carcinoid tumors metastasize. Metastases are much more common from the ileum than from the appendix, a fact probably related to the opportunities for growth before clinical recognition. In thirty carcinoid tumors of the ileum reported by Dockerty, thirteen had metastasized either locally or distantly. The metastases to the lymph nodes are yellow. Dockerty emphasized the frequency of perineural sheath invasion. Lymphosarcomas frequently involve regional nodes, and generalized involvement of many other nodes and organs usually takes place in advanced cases (Fig 396).

### Clinical Evolution

Many tumors of the small bowel give no symptoms and are discovered only at autopsy. Others produce signs and symptoms which vary according to the site, size, bleeding tendencies, and location of the tumor with regard to the lumen. The symptoms often suggest small bowel obstruction. Intermittent

times minute amounts of mucus can be seen within the cells (Dockerty). Tumor cells are frequently present within lymphatics. It is impossible to tell microscopically whether a carcinoid is benign or malignant, for the metastases also look exactly like the primary tumor. It is felt that they are probably all potentially malignant.

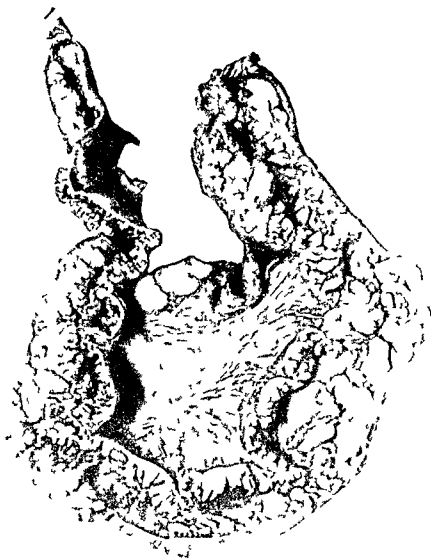


Fig 393—Gross specimen of extensive lymphosarcoma of the small bowel with typical giant rugae and widespread submucosal infiltration (courtesy of Dr A P Stout Department of Surgical Pathology Columbia University New York N Y)

The *lymphosarcoma* of the small bowel is almost as common as the adenocarcinoma. It occurs particularly in the ileum and often in young adult males. In a series of 109 lymphosarcomas of the intestine collected by Ullman, seventy-seven occurred in the small bowel, thirty-six of these in the ileum. The tumor may diffusely infiltrate the ileum over a fairly long distance (15 or 20 cm) and replace the wall with lymphoid masses. This lymphosarcoma of the small bowel may present discrete areas of involvement, diffuse involvement of the



Lymphosarcoma is difficult to diagnose. These tumors often cause considerable dilatation of the affected bowel, and it is very common to find regional lymph node involvement. If the tumor begins in the region of the ileum, inguinal lymph node metastases may mark the clinical onset, and later there will be generalization of the process. The symptomatology may either be very slow or very rapid in its evolution. Signs of intestinal obstruction, weakness, weight loss, and anorexia may appear. Bleeding into the gastrointestinal tract often results in a rather profound secondary anemia. Diarrhea, which does not respond to medication, is fairly common.

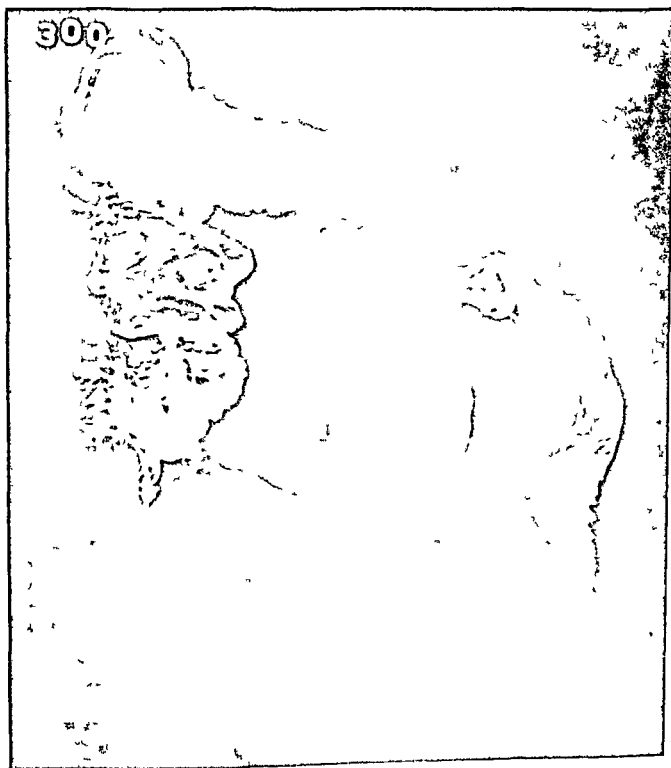


Fig. 394—Roentgenogram of an extensive lymphosarcoma of the ileum (garden-hose effect)

**Roentgenologic Examination**—The roentgenologic diagnosis of small bowel tumors is seldom made because of the rarity of the lesions and consequent lack of knowledge concerning techniques in examining the small bowel. If gastrointestinal studies of the esophagus, stomach, and large bowel are negative, and the symptoms persist, a careful roentgenologic examination of the small bowel should be done. The roentgenologic examination of the duodenum is facilitated by the fixity of the organ. The diagnosis is made on the basis of

tent pain, nausea occasional vomiting peristaltic rushes and borborygmi may occur Constipation and diarrhea may also be present As the obstruction becomes complete distention becomes marked, and vomiting at times fecal becomes persistent

Intussusception is a fairly frequent complication of small bowel tumors but its development depends upon the location of the tumor and whether it is polypoid or pedunculated Those tumors located in the submucosal regions particularly the lipomas (Schottenfeld) the pedunculated leiomyomas and polyps are prone to give this complication Intestinal obstruction was present in twenty seven of thirty nine myomas of the submucosal type reported by Smith (1937) The onset of the intussusception may be mild but the symptoms tend to recur bloody stools and a palpable mass are seldom present (Botsford) At other times the onset may be sudden and very painful and a tender mass is felt This intussusception rarely regresses spontaneously

Bleeding varying in amount may occur with any of these tumors The carcinoid for instance very rarely bleeds profusely but there may be mild hemorrhage due to superficial ulceration By contrast the leiomyoma whether benign or malignant often produces profuse repeated, alarming hemorrhages The subserosal tumor tends to grow quite large and liquefaction necrosis can occur with evacuation of the necrotic neoplasm into the intestinal lumen followed by a large hemorrhage Profound hemorrhages also occur in the cavernous type of hemangioma the adenocarcinoma and the lymphosarcoma

Bleeding results in secondary anemia Benign tumors are seldom the cause of death unless intestinal obstruction or intussusception develops with secondary peritonitis A few of the patients particularly those with leiomyomas may die of hemorrhage The spread of adenocarcinomas and other malignant tumors causes weight loss and other signs of deterioration of the general condition

### Diagnosis

**Clinical Examination**—The examination of a patient with tumor of the small bowel usually reveals little of significance A small bowel obstruction either partial or complete however may cause some distention peristaltic waves are visible and roentgenograms may reveal the typical signs Small bowel tumors are usually freely movable but only the very large tumor can be palpated Cameron in reviewing 200 malignant small bowel tumors found that 65 per cent of the sarcomas and 29 per cent of the carcinomas were palpable Intussusception may cause the formation of a fairly firm tender mass The presence of intussusception in an adult very frequently indicates the presence of a tumor About 25 per cent of all tumors in the region of the jejunoleum have this complication

Repeated intestinal hemorrhages without roentgenologic evidence of pathology in the esophagus stomach or large bowel may be a sign of tumor in the small intestine Hanco reported a leiomyoma of the jejunum which caused twenty episodes of bleeding over a fourteen year period Death occurred from the last hemorrhage and the diagnosis was made at necropsy

alterations in the mucosal patterns and the presence of obstruction, intussusception or extraluminal defects. The tumors which begin in the subserosal area, particularly the leiomyomas, often produce marked subtraction defects in a barium-filled bowel (Smith, 1937). Approximately one-fourth of the malignant tumors of the small bowel are nonobstructing and extraluminal. The roentgenologic findings may only show an irregularity of outline with obliteration of the mucosa and a variable dilatation throughout the lesion (Lingley). The involved area may be visualized after the passage of barium because the opaque substance adheres to the ulcerated wall. On radioscopic examination a mass may be felt in the area of the defect.



FIG. 97—Roentgenogram of cicatrizing enteritis involving terminal ileum and ascending colon.

The leiomyomas may have a central niche. If the mucosal defect is ragged rather than smooth, then a malignant neoplasm should be suspected. If there are multiple tumors with minimal ulceration and buckling in the region of the terminal ileum, then a diagnosis of multiple carcinoid should be considered (Miller). It is not infrequent for intussusception to take place between the ileum and the cecum. A case reported by Botsford showed valvulae conniventes of the small bowel inside the large bowel after evacuation. Weber and Kirklin emphasize that nonmalignant lesions tend to extend over longer segments of the bowel and that demarcation between the involved and uninvolved areas is gradual rather than abrupt, but that it is impossible in many instances to determine roentgenologically whether a given lesion of the small bowel is benign or malignant. Some lesions are well circumscribed and regular in



Fig 39 —Gross specimen of the ileum and appendix showing widespread submucosal involvement, thickening and superficial ulceration in a case of lymphosarcoma (same case as shown in Fig 394)



Fig 39 —Metastatic lymphosarcoma in the kidney from same case as shown in Fig 39

the surface of the small bowel from primary lesions of the stomach, pancreas, gall bladder, and peritoneal implants, even from breast and bronchus, can buckle the serosal surface, invade the wall, and ulcerate the mucosa. True metastases to the small bowel, particularly in the submucosa, are rare.

Primary melanocarcinomas of the small bowel probably do not occur for melanoblasts are not present. We agree with Herbut, that malignant melanomas of the small bowel are metastatic. It is not unusual to have such metastatic lesions occur from an unsuspected primary lesion of the skin or of the eye.

### Treatment

If a small bowel tumor is diagnosed from the clinical history, physical findings, and the roentgenologic examination, an exploratory laparotomy should be done. Before exploration, however, if there has been any degree of obstruction, the electrolyte balance should be restored by appropriate measures and if there has been any degree of bleeding, transfusions should be given. At the time of exploration the bowel can be opened and a biopsy made. At times, frozen section can determine whether the tumor is benign or malignant. If the lesion is located in the terminal ileum and there are large yellow metastases in the liver, frozen section usually shows the lesion to be a carcinosarcoma. Even in the presence of liver metastases, extensive surgical procedures are justified. If the tumor is malignant or if there is any question of neoplastic change, then a radical rather than a conservative operation should be done with removal of the accompanying mesentery and draining lymph node areas.

### Prognosis

If a benign tumor of the small bowel is completely resected, the prognosis is excellent. *Leiomyomas* may appear benign histologically but metastases can occur, therefore, a guarded prognosis should be given because clinically silent metastases may exist. The *adenocarcinomas* of the small bowel give an exceedingly poor prognosis because in practically every instance by the time the tumor is discovered, metastases to regional nodes and distant areas already exist. Of sixty-six patients with adenocarcinoma of the small bowel reported on by Mayo, only eight were alive and well five or more years after surgical treatment. If a *lymphosarcoma* is well localized to one segment of the bowel and perhaps to a few of the regional nodes, cure is possible. If a generalized process is present, the prognosis is poor. The average duration of life in eighty-five surgically treated patients with intestinal lymphosarcoma collected by Ullman was nineteen months. Ten were living and well five or more years after operation. *Carcinoids* of the small bowel give an excellent prognosis even if regional metastases are already present at the time of treatment, with resection of the primary lesion, these patients may live ten or more years.

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contour, but on microscopic examination may show evidence of malignancy. Weber and Kirklin report a high accuracy in diagnosis. Tumors of the duodenum were recognized roentgenologically in nine of seventeen cases, eleven of thirteen of the jejunum and four of six in the ileum were also recognized. They felt that roentgenologic recognition was most difficult in the ileum. In the small bowel a lymphosarcoma may involve a rather long segment of bowel giving a somewhat garden hose appearance (Fig. 394). The submucosa is implicated early in the evolution and the filling defect is clear cut. In sarcomas, Maissner has emphasized that the small bowel may show rigid walls irregular caliber of the lumen and lack of peristalsis.

**Laboratory Examination**—Patients suspected of having tumor of the small bowel should have examinations of the stools for the presence of occult blood.



Fig. 395.—Gross specimen of celiacizing enteritis involving the jejunum. There is narrowing of the lumen by hypertrophy of the muscularis and dilatation of the proximal segment.

**Differential Diagnosis**—Any lesion of the small bowel which gives signs suggesting small bowel obstruction may exactly simulate a tumor. A duodenal ulcer is the most common such lesion. The diverticula and Meckel's diverticulum, complications from an appendicitis, and regional ileitis may all simulate small bowel tumor. Other lesions in close proximity to the duodenum may cause defects in the bowel wall and thus an erroneous diagnosis of primary duodenal neoplasm may be made. These lesions include cysts and tumors of the pancreas, carcinoma of the hepatic flexure, and metastatic lesions of the retroperitoneal lymph nodes. Specific infections such as tuberculosis should be ruled out. Tuberculosis, however, is most prominent in the region of the ileum and invariably there is roentgenologic evidence of pulmonary disease. Celiacitis or enteritis occurs in young males and often shows multiple lesions and typical roentgenologic signs (Figs. 397 and 398).

**Secondary invasion of the small bowel by carcinomas arising in other organs** is particularly frequent. Carcinoma of the stomach can transgress the pylorus and involve the first portion of the duodenum. Carcinoma of the gall bladder transverse colon pancreas and common bile ducts can also invade the duodenum to ulcerate its surface and at times completely occlude it. Carcinoma of the large bowel may secondarily involve the small bowel. *Implantation on*

The appendix is formed from the outside by a serous layer, a muscular layer, a submucosa, and a mucosa. The mucous membrane is columnar epithelium with numerous large and small lymphatic nodules. Argentaffine cells are regularly present in the base of the glands.

**Lymphatics**—The lymphatics of the appendix gather into several collecting trunks which may terminate in the inferior nodes of the ileocolic chain or the posterior cecal nodes, or even in lymph nodes situated on the anterior surface of the third portion of the duodenum.

### Incidence

Tumors of the appendix are rare, the carcinoma type makes up approximately 90 per cent of the group, and about 80 per cent of them occur in females, with the greatest incidence in the third decade of life. The incidence of carcinoids in removed appendices is about 0.1 to 0.5 per cent. Adenocarcinomas usually appear in the fifth or sixth decades. Mucocoeles are more common in males than in females.

### Pathology

**Gross and Microscopic Pathology**—The *carcinoid* usually occurs in the distal end of the appendix, forms a submucosal mass, and quickly obliterates the lumen. This tumor tends to remain localized but it always has malignant potentialities. The *adenocarcinoma* occurs more frequently at the base of the appendix and forms polypoid masses usually growing within the lumen.

The *mucocoele* occurs primarily in the appendix, and, when localized to it, should be considered a benign lesion. If the appendix ruptures and tumor escapes into the peritoneal cavity, this tumor can grow and produce mucus, and, because of secondary changes produced, can cause death. In this sense, a mucocoele might be considered malignant. Woodruff believes that the pseudo-myxoma peritonei of appendiceal origin derives from a slowly growing cyst-adenocarcinoma of the appendix and that it cannot result from a benign mucocoele. Others, however, do not agree with this concept. In 43,000 appendectomies performed at the Mayo Clinic, 146 mucocoeles were found (Woodruff). The mucocoele results from obliteration of the distal portion of the appendiceal lumen probably by an inflammatory process. Even after obstruction, the lining epithelium continues to secrete mucus which gradually increases the size of the appendix and results in atrophy of the lining epithelium and thinning of the wall (Fig. 400). The average size of a mucocoele when first discovered is about 5 cm., but it may attain a huge size. Perforation may occur and the mucoid material may escape into the retroperitoneal area and form cysts or into the peritoneal cavity with formation of gelatinous implants. Following perforation, the appendix may collapse, the perforated area may heal, and a reaccumulation of mucus may form followed by a second perforation. Other complications such as gangrene or periappendiceal abscesses result. With growth of the peritoneal implants, intestinal obstruction may take place. Local invasion of other tissues, such as bladder and bowel, is not infrequent, but metastases to the regional lymph nodes do not occur. Acute peritonitis

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## TUMORS OF THE APPENDIX

### Anatomy

The appendix is a flexuous cylindrical structure 8 to 10 cm in length which is implanted on and communicates with the cecum. The appendix has a mesenteric attachment, the mesoappendix which carries in its free border the appendiceal artery, a terminal branch of the superior mesenteric artery. Because of the considerable variation in the development of the cecal area the normal position of the appendix is variable.



very frequently develops when pseudomyxoma peritonei is present In Table XIX are compared the three main types of appendiceal lesions

*Lymphosarcomas* may arise from the appendix (Knox), twenty-three primary lymphosarcomas having been reported Their appearance does not differ from that of lymphosarcomas found elsewhere

TABLE XIX DIFFERENTIAL CHARACTER OF THREE TYPES OF CARCINOMA OF APPENDIX  
(From Uihlein, A, and McDonald, J R Surg, Gynec & Obst, 1943)

	CARCINOID TYPE	CYSTIC TYPE	COLONIC TYPE
Location	Usually tip	Tip or base	Tip or base, more frequently base
Incidence	89 per cent	8 per cent	3 per cent
Gross character	Yellowish solid	Cystic, frequently on basis of a mucocoele	Gravish, polypoid or ulcerating
Microscopic structure	Poorly formed acini, mucosa intact over tumor, reduction of silver salts, affinity for chrome salts	Papillary projections originating in cyst, comparable to cyst adenocarcinoma of ovary, epithelial cells few because of destruction by mucus	Frequently well formed acini, mucous membrane ulcerated, comparable to carcinoma of colon
Mitoses	Few	Few	Variable
Mucus	None	Secretes large quantities	Secretes variable quantities
Metastasis	To regional nodes in less than 1 per cent	So called pseudomyxoma peritonei	To lymph nodes and liver

The microscopic appearance of the adenocarcinoma, carcinoid, and lymphosarcoma of the appendix is also similar to that presented by these lesions in other locations The mucocoele reveals atrophy of the lining epithelium and large collections of mucus, and peritoneal implants invariably show small collections of tall columnar cells secreting mucus

### Clinical Evolution

The evolution of all the tumors of the appendix is essentially the same Symptoms suggesting appendicitis occur with each one In the mucocoele, these symptoms may be of extremely long duration

### Diagnosis

**Clinical Examination**—The clinical examination usually reveals signs suggesting acute or subacute appendicitis The mucocoele presents a palpable mass and if pseudomyxoma peritonei is present, nodular abdominal masses may be evident The diagnosis of any neoplasm of the appendix is rarely made before exploratory laparotomy

Even at exploration, carcinoids and adenocarcinomas are very seldom even considered unless obvious tumor metastases have appeared A metastatic carcinoid in a regional lymph node may be yellow on section The mucocoele can be diagnosed on its very characteristic appearance it is uniformly swollen and the wall is thinned out A lymphosarcoma is practically never recognized at exploration

Fig 399



Fig 400

Fig 399—Large unruptured mucocoele of the appendix with uniform enlargement

Fig 400—Same specimen as shown in Fig 399 on cut section showing mucoid surface and obliteration of normal mucosal markings

major muscles. Inferiorly it commonly extends to a position overlying the right common iliac vessels. The ascending colon is retroperitoneal and lies posteriorly on the upper branches of the lumbar plexus, the transversalis fascia, and lateral border of the right kidney. Its upper limit is at the lower surface of the right lobe of the liver to which it is attached by a fold of peritoneum. The transverse colon is also a peritoneal portion of the large bowel and is attached to the posterior abdominal wall by the transverse mesocolon. The attachment of the mesocolon crosses the perinephric fascia of the right kidney at the level of the hilum, the second portion of the duodenum, and the head of the pancreas approximately at the level of the second lumbar vertebra, to become parietal peritoneum along the entire length of the body and tail of the pancreas and thereby crossing the left kidney fascia at a somewhat higher level than the right. From the splenic flexure, the colon becomes retroperitoneal. The relationships of the descending colon are very similar to those of the ascending colon. The descending colon becomes the sigmoid colon at the point where the mesosigmoid begins. This mesenteric attachment normally assumes the shape of an inverted V. The attachments of the mesosigmoid to the pelvic wall have a posterior relationship with the endopelvic fascia and, in the pelvis, cross the left ureter. The right limb of the mesentery usually is in relation only to the posterior hemorrhoidal vessels and the presacral portion of the pelvic fascia. The rectum begins at the termination of the mesosigmoid, at which point the peritoneum invests the intestine only on its sides and anterior surface. The rectum occupies the sacrococcygeal curvature and has at least three definite lateral flexures. The peritoneal covering is reflected laterally from the rectum to form the perirectal fossa and anteriorly the rectovesical or uterine fold. The lower part of the rectum, known as the rectal ampulla, is devoid of peritoneum. This extraperitoneal segment is in relation to the floor of the pelvis posteriorly, and to the prostate, seminal vesicles, and rectovesical fascia anteriorly in the male, or to the posterior wall of the vaginal canal in the female.

The blood supply of the large bowel comes from three major sources: (1) the superior mesenteric artery, (2) the inferior mesenteric artery, and (3) the branches of the internal iliac artery (middle hemorrhoidal, inferior hemorrhoidal, and pudic). An understanding of this blood supply is very important when the surgical treatment of cancer of the large bowel is undertaken.

The ascending colon, the hepatic flexure, and most of the transverse colon are supplied by the superior mesenteric through its right colic and middle colic branches. The splenic flexure, the descending colon, the sigmoid, and the upper half of the rectum are supplied by the left colic and sigmoid branches of the inferior mesenteric artery. The superior hemorrhoidal artery is a terminal branch of the inferior mesenteric. The lower half of the rectum and the anus are supplied by the middle hemorrhoidal artery (from the internal iliac) and the inferior hemorrhoidal artery (from the internal pudic branch of the internal iliac). These main arterial branches present numerous anomalies. The surgical repercussions of these anatomic changes have been studied by Singleton.

**Differential Diagnosis**—The most important differential diagnosis is *ap pendicitis*. The only differentiating feature is that the mucocoele may form a mass, which, however, may be confused with a perirappendiceal abscess. At times, roentgenologic examination reveals calcification within a mucocoele. A pseudomucinous tumor of the ovary may be associated with a mucocoele.

### Treatment

A simple excision of a carcinoid which is confined to the tip of the ap pendix is sufficient treatment. With an adenocarcinoma of the appendix, it may be necessary to resect radically the cecum and attached mesentery in order to remove all the possibly involved regional lymph nodes. The mucocoele should be carefully resected. If the mucocoele has perforated and pseudomyx oma peritonei is present, all that can be done is to remove as much gelatinous tumor as possible.

### Prognosis

The prognosis of the well localized carcinoid and the unperforated mucocoele is excellent. An adenocarcinoma of the appendix with no regional metastases also has a good prognosis. If pseudomyxoma peritonei is present, the prognosis is poor, although the duration of life may be long. Lymphosarcomas of the appendix also have a relatively poor prognosis except for the polypoid group which are often relatively benign.

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## CARCINOMA OF THE LARGE BOWEL

### Anatomy

The large bowel, the terminal portion of the gastrointestinal tract, extends from the ileocecal valve to the anus. It originates in the right iliac fossa (the cecum) from where it ascends vertically to the lower surface of the liver (ascending colon) to change direction in a right angle (hepatic flexure) and follows a transversal direction from right to left (transverse colon) until it reaches the spleen where it again changes its course at a rather marked angle (splenic flexure) to follow a vertical direction (descending colon) toward the left iliac fossa. Then it curves upon itself in the form of a letter "S" (sigmoid colon) to reach the anterior aspect of the sacrum (rectum) and its termination in the anus.

The cecum is a peritoneal part of the large bowel. It extends from the appendix to about the level of a transverse plane passing through the iliac crest. Posteriorly it is in relation to the femoral nerve and iliacus and psoas

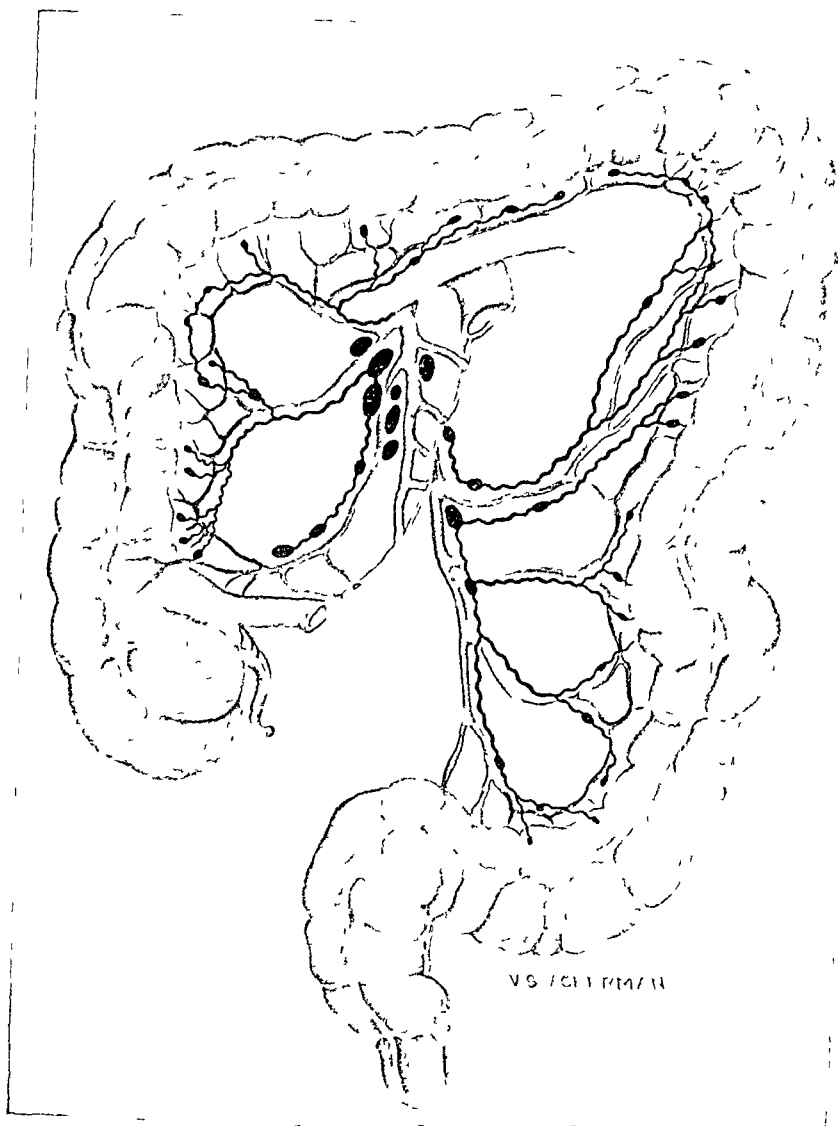


Fig 401—Anatomic sketch of the lymphatic drainage of the colon. The territory of the superior mesenteric artery is drained by the central superior mesenteric group of lymph nodes while the region of the inferior mesenteric is further drained by lateroaortic nodes

Branches of the mesenteric arteries form a continuous vessel within the circle of the colon, forming a marginal arch at a fairly constant distance from the mesenteric border. From this arch, the vasa recta originate to pursue a straight course, entering the mesenteric border of the bowel without anastomosing with one another. The anastomosis of blood vessels within the bowel wall is not very frequent and consequently the blood supply is deficient. The part of the colon located between the taenia is very poorly supplied but does receive some blood from the terminal vessels on either side.

**Lymphatics**—The lymphatics of the *cecum* are divided into anterior and posterior groups which empty into the nodes of the ileocolic chain.

The abundant subserous network of lymphatics of the *colon* is drained, for the most part, by the paracolic lymph nodes, but some among them do not stop at this first relay and continue to the intermediate group of lymph nodes or even directly to the mesenteric or lateroaortic nodes (Fig 401). The segment of the colon which is supplied by the superior mesenteric artery drains its lymph in the satellite lymph nodes of the right colic artery or in the central superior mesenteric group of lymph nodes. The part of the colon which is supplied by the inferior mesenteric has two different lymphatic connections: (1) a superior segment drained by the central superior mesenteric group of lymph nodes and (2) an inferior segment drained by the lateroaortic nodes.

The lymphatics of the *ascending colon* empty into the paracolic lymph nodes but a few may communicate with the perirenal lymphatic pathways. The lymphatics of the right side of the *transverse colon* (the right two thirds or three fourths) terminate in the paracolic lymph nodes. Some empty into the nodes accompanying the middle colic artery and thence into the central group of the superior mesenteric chain. The lymphatics of the remaining one third or one fourth of the transverse colon drain into the paracolic chain and finally into the central nodes of the superior mesenteric artery. The lymphatics of the *descending colon* are drained by the lymph nodes along the left colic artery and then by the nodes of the inferior mesenteric chain. The collecting trunks of the sigmoid colon empty into the lymph nodes accompanying the sigmoid and inferior mesenteric artery to terminate in the para-aortic lymph nodes.

The lymphatics of the *rectum* have numerous anastomoses with those of the prostate, seminal vesicles, vagina, bladder, and the levator ani muscles. They are divided into inferior, middle and superior trunks.

The *inferior collecting trunk*s originate in the cutaneous part of the anus and drain into the superficial inguinal lymph nodes.

The *middle collecting trunk*s usually follow the middle hemorrhoidal vessels and terminate in the hypogastric lymph nodes. They may also accompany the lateral and medial sacral arteries and drain into the nodes of the promontory and of the sacrum (Fig 402).

The *superior collecting trunk*s extend through the entire length of the rectum and empty into the anorectal lymph nodes which are found along the course of the superior hemorrhoidal blood vessels. They finally terminate in the nodes which are found at the level of the bifurcation of the inferior mesenteric artery. These are by far the most important lymph nodes draining the

rectum Some of these trunks may end in a node in the region of the inferior mesenteric artery, near the point of origin of its lower sigmoid branch, without stopping at the nodes of the bifurcation There are also long collecting trunks which arise from the lower portion of the rectum and terminate without interruption in lymph nodes at the summit of the pelvic mesocolon or pre-aortic and latero-aortic lymph nodes (Rouvière)

### Incidence and Etiology

In the gastrointestinal tract, carcinoma of the large bowel is second in frequency only to carcinoma of the stomach In Dukes' series of 1,000 cases, 650 were males and 350 were females The majority of the cases occurred between 50 and 70 years, only 6 per cent of the males and 11 per cent of the females were under 40 years

The most important single etiologic factor concerning carcinoma of the large bowel is the presence of *polyps* They are about twelve times more frequent in the large bowel than in the small bowel (Lawrence) It is impossible to determine with any degree of accuracy how many cases of carcinoma of the large bowel arise from pre-existing polyps, for in many instances the lesion is well advanced when it is first seen and the site of origin is consequently obscured (Fig 406) It is probable that higher rather than lower percentages arise on this basis (estimated 15 to 40 per cent) The incidence of polyps in patients with carcinoma of the large bowel is much higher than in those without this form of cancer It is not too unusual to find multiple distinct primary carcinomas or to discover several polyps coexisting with a carcinoma (Fig 404) The polyp is the most common benign tumor of the large bowel in 1,400 consecutive necropsies, Helwig found eighty cases of single polyps and fifty-nine cases with two or more polyps, or a total incidence of 9 per cent Helwig noted that 44 per cent of the polyps occurred in the sigmoid colon and rectum and that the rest were distributed throughout the remainder of the large bowel (Table XX) This high proportion of sigmoid and rectal lesions also parallels the high incidence of carcinoma of the large bowel in this region Hullsiek collected 128 cases of multiple polyposis of the colon in which forty-six of the patients developed carcinoma Polyposis can be either acquired or congenital (Fig 407) Several cases may be found in the same family (McKenney)

TABLE XX DISTRIBUTION OF POLYPS IN LARGE BOWEL  
(From Helwig, E B Surg, Gynec & Obst, 1943)

	CASES	PERCENTAGE
Cecum	32	12
Ascending colon	42	15
Hepatic flexure	12	4
Transverse colon	32	12
Splenic flexure	13	5
Descending colon	22	8
Sigmoid colon	76	28
Rectum	43	16
Total	272	

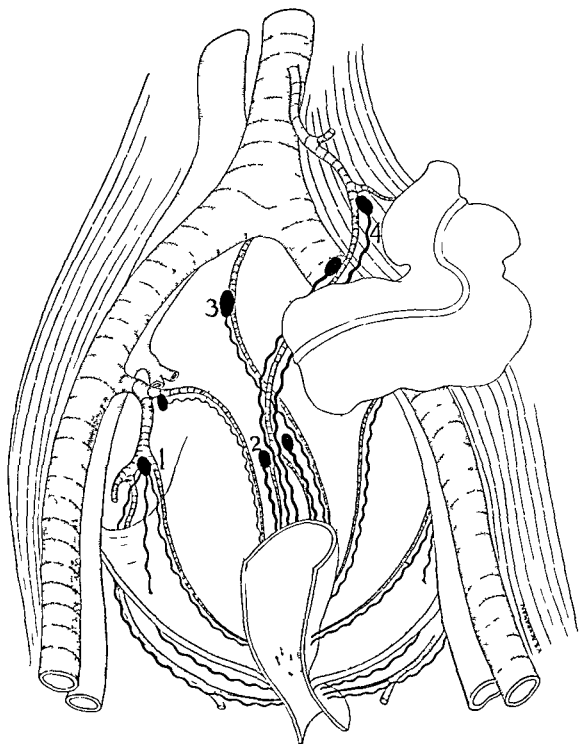


Fig. 40\*—Anatomic sketch of the lymphatics of the rectum. Inferior collecting trunks are drained by inguinal nodes. The middle collecting trunks are drained by 1 hypogastric nodes, 2 sacral nodes, and 3 nodes of the promontory. The superior collecting trunks are finally drained by 4 the nodes at the bifurcation of the inferior mesenteric artery.



largest in areas where there is the greatest space for their development, such as in the cecum. Their surface is usually ulcerated and as they enlarge in size, they tend to show a deep central ulceration with overhanging margins. They may become completely circumferential and produce partial or complete obstruction of the bowel. With obstruction the proximal large bowel may dilate and the muscularis becomes hypertrophied. On section grayish-yellow tumor can often be seen replacing the muscular layers of the bowel. These carcinomas can also be flat and deeply ulcerating. The mucinous type of carcinoma of the bowel may show a rather pebbly overlying mucosa with some degree of submucosal extension (Fig. 408). Often on section, mucoidlike material can be observed.

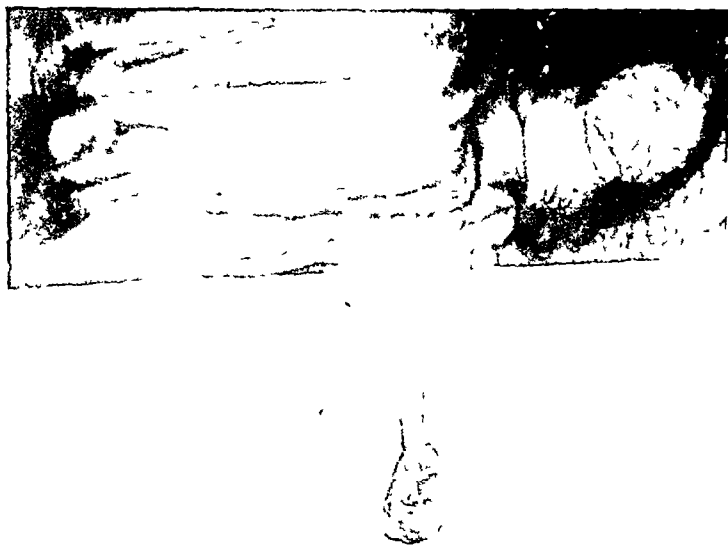


Fig. 404 — Benign polyp (pedunculated type) found in a surgical specimen from an abdominoperineal resection for carcinoma of the rectum.

Multiple carcinomas of the large bowel are not too uncommon. Beison found seventy-nine patients with two carcinomas and nine with three. The frequency of multiple carcinomas in this group was 4.6 per cent.

Carcinomas of the large bowel tend to spread locally and to reach the serosal surface of the bowel where infection plus tumor causes adherence to neighboring organs. Fixation often means tumor extension. Carcinoma of the cecum may directly invade the lateral abdominal gutter and, at times, the anterior abdominal wall. Involvement of the pancreas, gall bladder, liver, spleen and wall of the stomach may also occur. Fixation however, is most common in the region of the rectum and sigmoid. In males, bladder invasion is common but only rarely does true invasion of the prostate occur. Denon

Lynn collected ninety five cases of *chronic ulcerative colitis* in children in which six (6.3 per cent) subsequently developed carcinoma, and in a total of 1,467 patients with chronic ulcerative colitis, twenty eight (2 per cent) later developed carcinoma. Four cases of carcinoma of the colon reported by Reed followed chronic amebiasis. *Diverticula* increase in frequency with age but their presence in conjunction with carcinoma is infrequent. There is no proof that it is an etiologic factor.

### Pathology

**Gross Pathology**—Carcinoma of the large bowel has a fairly characteristic distribution. Sixty to seventy five per cent of the lesions are found in the rectum or rectosigmoid area. Boehme studied the distribution of 1,457 cases of malignant tumors of the large bowel removed at operation at the Lahey Clinic from 1936 to 1944. Seventy five per cent of the lesions were found in the sigmoid, rectosigmoid, and rectum with the remaining 25 per cent about

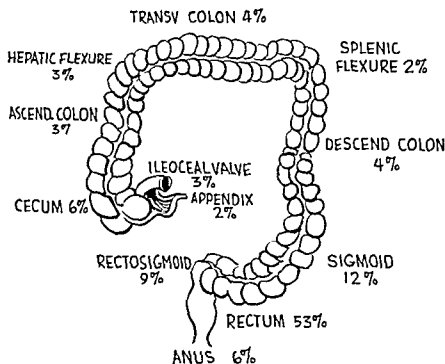


Fig 403—Study of the distribution of 147 malignant tumors of the large bowel (From Boehme L. S. Clin. North America, 1946)

equally distributed in the rest of the colon except for a slightly greater number at the level of the cecum (Fig 403). In 1,401 cases of carcinoma of the rectum and rectosigmoid, Bacon found that the sigmoid contained 22 per cent, the rectosigmoid 16 per cent, the rectum 56 per cent, and the anal canal 5 per cent.

Early carcinoma of the large bowel is well delineated and may show evidence of origin from a pre-existing polyp (Fig 405). Helwig (1947) demonstrated that carcinoma could also spring directly from the mucosa. These carcinomas are more frequently fungating than deeply ulcerating. They tend to grow the

vulva's fascia usually provides a protective check to intraprostatic invasion. In both sexes local extension usually first develops anteriorly. Posterior extension to the sacrum invariably means advanced disease. In females tumor rather frequently invades the vagina where it may present an ulcerating mass. Bladder invasion in females is relatively infrequent for the pelvic organs form an effective but vulnerable barrier.



Fig. 407.—Post-mortem specimen in a case of congenital polyposis. Numerous other members of the family had proved polyposis or had carcinomas of the bowel.

**METASTATIC SPREAD.**—The lymph node involvement in carcinoma of the rectum is extremely important because of its relation to prognosis. The tumor metastasizes in an orderly fashion from node to node and can progress up along the aorta as far as the mesenteric and peripancreatic lymph node areas. It can spread by means of the thoracic duct even to the supraclavicular nodes. If high nodes are involved, all intervening nodes leading from the primary

Fig 40a



Fig 40b

Fig 40 —Carcinoma and a sessile polyp arising in the same specimen as shown in Fig 40a

Fig 40c —Advanced fungating carcinoma of the rectum. Its possible origin from a polyp can no longer be identified. Same surgical specimen as shown in Figs 40a and 40b

grossly to be negative, eighteen contained carcinoma on microscopic examination, in 337 lymph nodes thought to be positive grossly, metastases were actually present in only 132

Perineural sheath invasion usually indicates advanced disease. In 100 patients with carcinoma of the rectum examined by Seefeld, there was lymph node involvement in forty-seven, perineural sheath invasion in thirty, and vein invasion in twenty.



FIG. 409.—Pedunculated benign polyp of the large bowel (x113 low-power enlargement)

Spread of the disease through the venous system is fairly frequent in carcinoma of the large bowel and results in metastases to the liver and lungs and eventually to bones, suprarenal glands, and other organs. The undifferentiated carcinoma of the large bowel metastasizes more freely than the differentiated carcinoma.

**Microscopic Pathology**—The microscopic appearance of carcinoma of the large bowel is that of a usually fairly well-differentiated adenocarcinoma which shows variable degrees of mucoid degeneration (Figs 412 and 413). The early signs of malignant change in the glands of the large bowel, such as occur in a polyp, include stratification of cells, loss of nuclear polarity, and mitotic figures.

lesion will be found replaced by tumor. Rarely does a tumor by pass any lymph node group. Retrograde involvement of lymph nodes does not take place until the nodes surrounding and above the tumor are completely involved (Gilchrist). The examination of forty six surgical specimens of carcinoma of the colon showed an average of fifty two nodes per specimen and evidence of lymph node involvement by carcinoma in 61 per cent (Coller). There is usually no relation between the size of the node and the presence of carcinoma within it, nor does the size of the tumor bear any relationship to the lymph node involvement.



Fig 408—Mucinous carcinoma of the bowel with hypertrophy of the muscularis and pebbly overgrowth of the involved mucosa.

It may be difficult to determine grossly whether a given node contains tumor but the error of this macroscopic appreciation is small if the nodes appear negative. However, the hard consistency and the enlargement of the nodes are often due merely to inflammation and not to metastatic disease. The following figures of Gabriel prove this point. of 905 lymph nodes considered

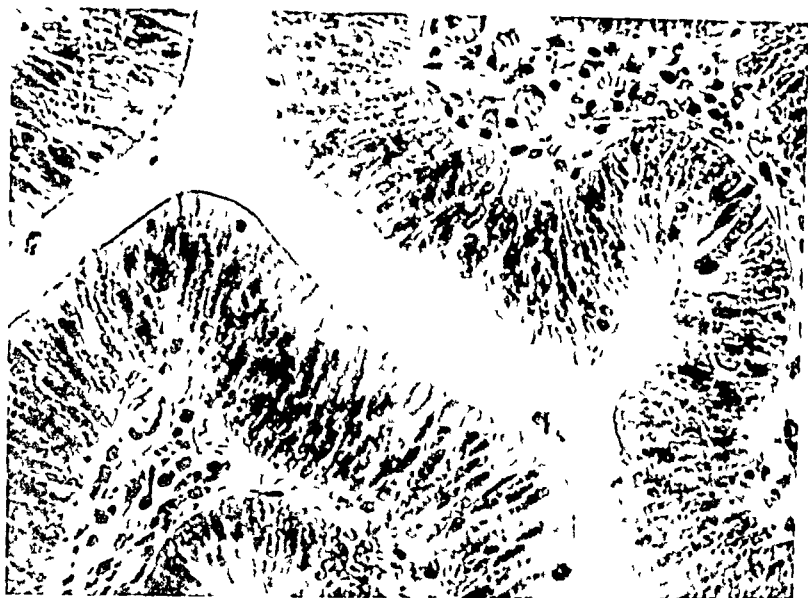


Fig. 411 —Photomicrograph demonstrating the earliest malignant changes seen in a polyp. Note stratification of cells, loss of nuclear polarity, and mitotic figures (high-power enlargement).



Fig. 412 —Photomicrograph of an adenocarcinoma of the rectum (moderate enlargement).

(Fig 411) Nuclei are often deep staining with prominent nucleoli. Intra glandular budding may be present and invasion is recognized when there is no longer a definite border between epithelial cells and stroma (Helwig, 1947). The few very undifferentiated adenocarcinomas of the colon may be hard to recognize (Fig 414). In rare cases, the tumor may show mucin production within its cells (signet ring type) and in these instances the tumor tends to extend submucosally, grows quietly through the wall, often obstructs and develops early metastases. Perineural sheath invasion is seen as small nests of tumor cells lying within the distended sheath of nerves. Blood vessel invasion should also be searched for particularly in submucosal and serosal areas. The more undifferentiated the tumor, the higher the proportion of blood vessel invasion.

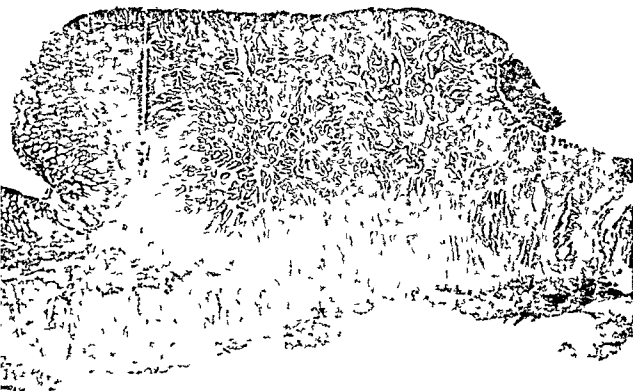


Fig 410—See the polyp partially replaced by a carcinoma that has already invaded the muscularis (low power enlargement)

Vein invasion is invariably demonstrated microscopically when there is metastatic carcinoma within the liver. Grinnell reports that vessel invasion before complete penetration of the muscular wall of the large bowel is rare. This invasion should be substantiated by special stains to prove that tumor is within a vessel. Brown indicated that at least three sections of the main tumor should be taken.

### Clinical Evolution

The clinical development of carcinoma in the different sections of the colon and rectum offers nothing, but nuances within the syndrome common



tients with carcinoma of the rectum, made a summary of the symptoms before admission as follows

	FIRST SYMPTOM	NOTED BEFORE ADMISSION
Blood in the stools	52	87
Constipation	30	51
Flatus (foul)	28	47
Diarrhea	12	36
Pain	4	36
Mucus in stools	1	31
Weight loss	0	20
Change in size of stools	0	18
Tenesmus	0	14
Obstruction	0	8
Anorexia	1	1

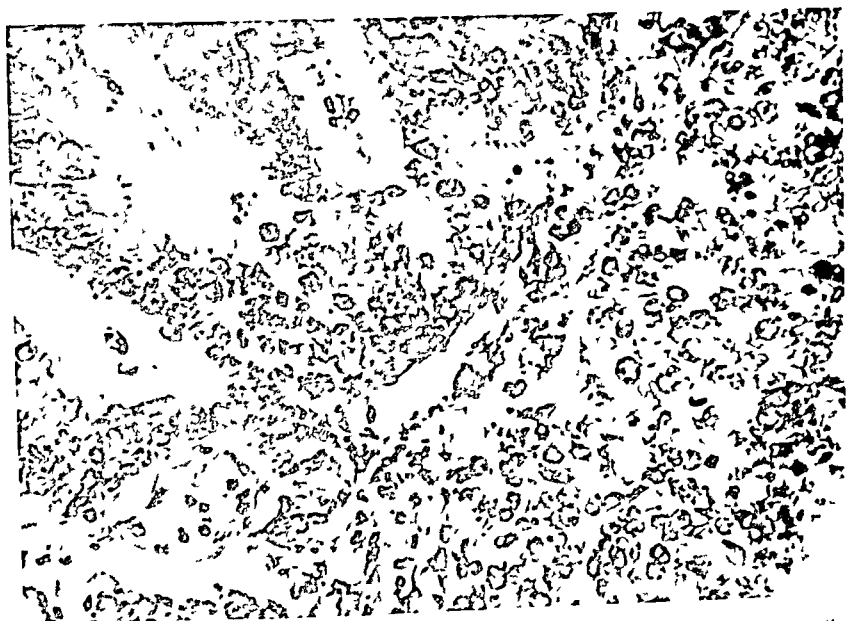


Fig. 111—Relatively undifferentiated adenocarcinoma of the rectum. Some areas have lost the adenoid arrangement (moderate enlargement)

The lesions in the various parts of the large bowel do show some differences. The tumors in the descending colon, particularly sigmoid and rectum, frequently give symptoms of obstruction. Obstruction of the left colon is about eight times more frequent than right colon. The carcinomas of the right colon obstruct only when they become large and most frequently cause abdominal pain. This pain is usually intermittent, tends to become more constant, and is typically not severe (Connor). Weakness is often also associated with carcinoma of the right colon. Changes in bowel habit are present in about two-thirds of the cases. Carcinomas arising in the cecum tend to grow

to all carcinomas of the large bowel. In almost every instance it produces either an insidious alteration in bowel habits (constipation or diarrhea), pain and nausea from obstruction, or blood in the stool (Lahey). Rectal tenesmus may coexist with the constipation. A minimal obstruction may cause some distention, but as the obstruction progresses, peristaltic waves attempt to pass fecal material through the opening, causing spasmodic attacks of pain, "gas pain," and constipation and alternate attacks of mucous diarrhea. At times there may be a complete block with distention and fecal vomiting. The obstruction is usually progressive but it may occur suddenly as a consequence of



FIG. 113—Adenocarcinoma of the rectum with prominent mucin production (moderate chromatinment)

intussusception or ingestion of barium. Without obstruction the patient usually looks and feels well and does not lose weight. Rectal bleeding may be observed early. Usually the elimination of blood occurs before defecation but may take place in the intervals between stools. Sometimes the blood may pass unnoticed mixed with the fecal material or mucus. Bleeding may be more marked with cecal lesions. With continual bleeding anemia and weakness appear. Intense sacrospinal pain may be caused by extension of the tumor to the sacrum and sacral plexus. If the tumor metastasizes the weight loss may quickly reach twenty-five or thirty pounds. Braund, in a report on 108 pa-

the cul-de-sac, rectum, or sigmoid. Vagino-rectal examination gives additional information in women, particularly when the lesion is located on the anterior wall of the rectum.

Rectal palpation should determine how much of the circumference of the bowel wall is involved and whether the tumor is polypoid or deeply ulcerating. Its level in regard to other organs such as the cervix, uterus, or prostate should be ascertained. In both males and females, an effort should be made to determine fixation, anterior and posterior, for its presence or absence bears considerable relationship to the operability and prognosis.

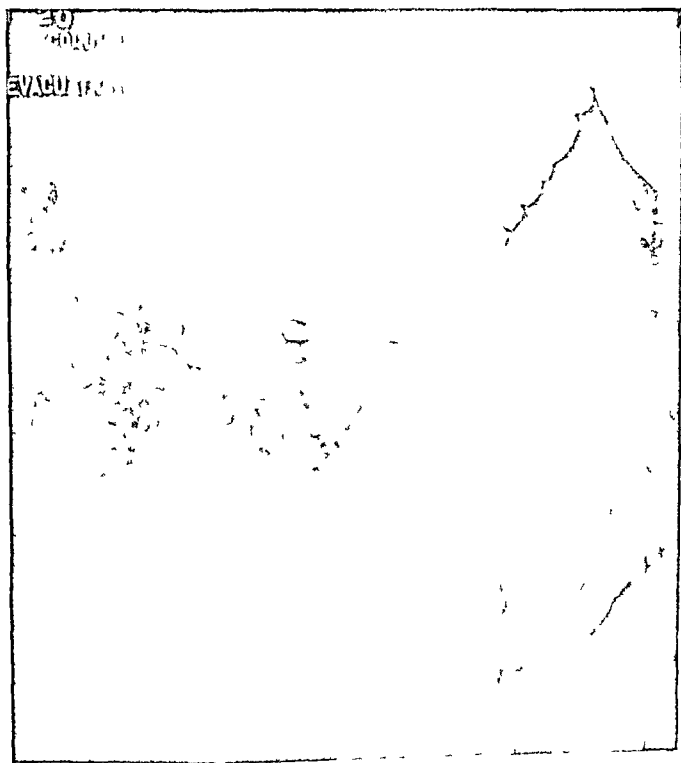


Fig 415—Roentgenogram of a carcinoma of the cecum. Note filling defect after barium enema.

In intestinal polyposis there may be more than one carcinoma. Since this disease is often familial, all immediate members of the family should have proctoscopic examination and barium enema. The patients apparently cured of carcinoma of the large bowel have a higher chance of developing new tumors of the large bowel than other individuals of the same age. For this reason they should be followed indefinitely and repeat barium enemas at proper time intervals are indicated.

very large and often produce no symptoms of obstruction but may present an old cure profound anemia, related perhaps to the large bleeding surface of a fungating tumor

With spread of the disease particularly if it is located in the lower bowel, pain may radiate down the thighs into the perineum, obstruction of the ureters may occur, and death is then due to uremia. In other instances, complete bowel obstruction may appear, and death may follow because of perforation and terminal peritonitis. The formation of fistulas with growth of the carcinoma into the bladder, peritoneal cavity, or abdominal wall occurs very rarely. In a few instances, when extensive local and distant spread of the disease has developed death may supervene from a combination of factors. Hypoproteinemur anemia hemorrhage and terminal bronchopneumonia often contribute to the terminal picture.

### Diagnosis

**Clinical Examination**—The physical examination of a patient with carcinoma of the colon or cecum often reveals very little. At times, a palpable slightly tender movable mass is felt.

There is a variable number of patients without specific symptoms which can be ascribed to large bowel lesions. They may have obscure weight loss and anemia. This anemia may be severe particularly with lesions which have a large ulcerating surface such as those arising in the cecal area. If the cause of the anemia is not clear cut, abdominal examination may reveal a palpable mass in the cecal region and a stool examination for occult blood will be positive.

The inspection and palpation of the abdomen frequently show some meteorism, particularly in the cecal region, regardless of the site of the lesion. It is important to know that spasmodic pain usually centers in a part of the bowel well above the lesion, not infrequently in the cecal region because of distention. Hemorrhoids may coexist and even develop because of a carcinoma of the rectum. This should be remembered before making a rapid diagnosis of hemorrhoids in an aged patient.

It is regrettable that there is so often considerable delay between the first symptom of a rectal carcinoma and its appropriate treatment. Too frequently rectal examination is not done. Of 100 patients with carcinoma of the rectum sent by family physicians for surgical treatment diagnosis and referral were made within a month in only twenty four. In seventy five there was a ten month delay before admission to the hospital was sought. The interim was consumed by inadequate or improper treatment (Birund). It should be strongly emphasized that if a carcinoma is located in the low sigmoid or rectum it can be felt rectally on digital examination. Seventy five per cent of all carcinomas of the large bowel can be found by this method. In the rectal palpation the examining finger should sweep over the rectal mucosa as high as possible. Sheddien feels that in the Sims' position (laterodecubitus) the examining finger can reach higher than in the knee chest or the knee shoulder position. A squatting position may at times bring down a prolapsing lesion in





Fig 416—Surgical specimen of the same lesion illustrated in Fig 415, showing large typical fungating carcinoma of the cecum which had not yet metastasized to regional lymph nodes

symptoms in rare instances when the tuberculosis is hyperplastic, the roentgenologic examination may also demonstrate involvement of the ileum, and this indirect sign is often helpful in the differential diagnosis. A roentgenologic examination of the lungs may or may not show active tuberculosis, but when it is not present, the diagnosis becomes more difficult.



Fig 418—Foreign bodies (orange seeds) in the region of the cecum resulting in inflammation, ulceration and tumefaction which was confused roentgenologically and at exploration with carcinoma and was resected.

If a *foreign body*, particularly in the region of the cecum, ulcerates and obstructs the bowel, it may form a mass which is difficult to differentiate from carcinoma (Fig 418). *Diverticulitis* and *diverticulosis* occur particularly in the region of the sigmoid and may give symptoms and signs suggesting large bowel carcinoma. Bleeding sometimes occurs and the diverticula may become infected. With infection, a pericolic abscess may form to cause the development of inflammatory masses which may be thought malignant. *Diverticulitis* may give symptoms in either side of the abdomen and in a few instances is extremely difficult to differentiate from carcinoma roentgenologically (Schatzki). The roentgenologic demonstration of diverticula does not rule out carcinoma,

ber of instances may materially alter or even contraindicate proposed surgical procedures. A lesion which resembles carcinoma may prove to be inflammatory or represent a benign rather than a malignant neoplasm. In general for lesions of the colon, the pathologic diagnosis must await the examination of the surgical specimen.

**Differential Diagnosis**—Carcinoma of the large bowel may not be suspected if there are no specific symptoms pointing to it, but when suggestive evidence of its presence is encountered there are various specific lesions of the large bowel with which it must be differentiated. The clinical points of differentiation are often vague and the roentgenologic examination is by far the best method of distinguishing the various lesions.



Fig 41"—Marked irregular filling defect of the rectosigmoid due to carcinoma

If a carcinoma arises in the cecum, the symptoms suggest *appendicitis* with right lower quadrant pain and perhaps tenderness. About 25 per cent of the patients are operated on with this preoperative interpretation. *Any patient, but particularly a male over 50 years of age with symptoms suggesting appendicitis should be examined carefully.* If a mass is present and there is evidence of anemia, weight loss and occult blood in the stool carcinoma rather than appendicitis should be considered and a barium enema done. Carcinoma of the cecum may also suggest *peptic ulcer, gall bladder disease, or kidney tumor.*

A peptic ulcer and gall bladder disease may be ruled out by roentgenologic study and the history. A kidney tumor extends toward the retroperitoneal region and usually cannot be moved laterally. A carcinoma of the cecum can be palpated to the side and is felt in a lower region than the kidney tumor. The retrograde pyelograms may show displacement of the ureter by a cecal mass but the kidney itself and its pelvis are normal.

The usual *tuberculosis* of the large bowel does not mimic carcinoma inasmuch as it involves both ileum and cecum, with multiple areas of ulceration and considerable spasm and is usually accompanied by pulmonary disease. Tuberculosis in the ileocecal region of the large bowel can cause obstructive



and, conversely, they may fail to fill and will not be roentgenologically demonstrated by barium enema. When there is constriction of the lumen due to secondary infection and inflammation (Fig 419), the constriction varies from moment to moment, unlike that of a malignant lesion, in addition, the mucosal contours persist or are exaggerated, producing a very irregular, jagged, saw-tooth margin (Golden). In case of complete obstruction, however, no differential diagnosis can be made. The acute variety of ulcerative colitis is not hard to diagnose. Chronic localized areas of *ulcerative colitis* and pericolic inflammatory masses may promote some question, for they can present a filling defect and inflammatory masses (Fig 420). Thus, at times, may be resolved by careful roentgenologic examination.

*Benign tumors* of the large bowel develop fairly frequently. Helwig found 139 polyps, thirteen lipomas, one carcinoid, and one leiomyoma. Polyps may have several forms, but they are usually well delineated from the surrounding healthy mucosa and are either sessile with a broad base or are pedunculated with a stalk. Frequently they are multiple. True polyps usually have a pedicle made up of a fragile stalk of glandular branching epithelium in which the muscularis mucosa is at times invaginated. They may grow from a barely perceptible tumor to one several centimeters in size. Saint believes that most of these tumors first show malignant change in the distal end. Helwig, however, is of the opinion that the initial malignant change occurs at any point. Polyps may cause bleeding, chronic diarrhea, and increased mucus in the stool, and if the polyp is low lying, there may be marked morning urgency to defecate (Slaughter). Polyposis causes fairly distinctive symptoms and signs which Erdmann divides into an adolescent and adult type. The adolescent type (12 to 20 years) is associated with intestinal hemorrhage and diarrhea, presents lesions extending down to the anus, and occurs in both males and females of the same family. The adult type is secondary to and associated with inflammatory lesions. Hallsiek reported 127 cases of the adolescent type, 66 per cent appearing between the ages of 15 and 35 years, and almost equally distributed in both sexes. Carcinoma developed in forty-two, and in thirty-one others death was caused questionably by carcinoma.

The lipomas are most frequently located in the submucosa of the cecum and ascending colon (twelve of thirteen cases) (Helwig). Leiomyomas and carcinoids are uncommon in the large bowel (Stout). The microscopic appearances of the leiomyomas and lipomas do not differ from those found in the small bowel. Carcinoids appear most often in the rectum and may be benign, while when located above the sigmoid, they are frequently malignant. They are similar in nature to the carcinoids of the appendix and ileum (see Tumors of the Small Bowel).

*Lymphosarcoma* is relatively infrequent in the large bowel. In a series of 109 cases of lymphosarcoma of the intestines collected by Ullman, only thirty-two originated in the large bowel. It appears predominantly in males between 40 and 50 years of age and may cause the same gross variants which are observed in the stomach (polypoid masses, disclike areas, and prominent folds resembling cerebral convolutions). Its microscopic appearance is simi-



Fig 419—Multiple diverticula of the sigmoid colon with adjacent diverticulitis producing tumor like swelling of the bowel wall and pericolic abscess (From Golden R New England J Med 1934)

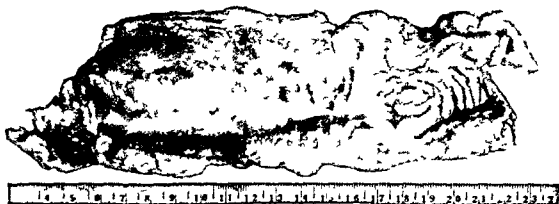


Fig 420—Surgical specimen of an area of chronic ulcerative colitis in the region of the splenic flexure which, because of a mass and roentgenologic findings was confused with carcinoma

gans. The lungs are involved in more than one-half of the cases. Melanin is also found in the urine, particularly when liver involvement is present. Chabot emphasized that the best treatment for this type of malignant tumor is wide excision with routine bilateral groin dissection, even if there is no enlargement of the lymph nodes.

The *sacrococcygeal chordoma* is a relatively rare tumor which occurs most frequently in males between the ages of 45 and 50 years. It may at times be confused with carcinoma of the rectum or rectosigmoid area. It begins in the sacrococcygeal area and may slowly surround and obstruct the large bowel. However, it practically never ulcerates the lumen. Roentgenographic examination invariably shows destruction of the sacrum. A biopsy will reveal the typical (Fig. 422) microscopic picture (Mabrey).



Fig. 422—Typical physaliphore cells of a sacrococcygeal chordoma. The patient was referred with a diagnosis of carcinoma of the rectum. Note cytoplasmic vacuolation due to glycogen.

Other tumors in the region of the anus include squamous carcinoma and rarely carcinoid. Superficially ulcerated hidradenomas close to the anal orifice may cause confusion in diagnosis. It is not too unusual for other inflammatory lesions such as tuberculosis, lymphogranuloma venereum, or even amoebic granuloma in this region to simulate carcinoma. An infectious granuloma which destroys the mucosa cannot be differentiated roentgenologically from carcinoma (Gunn and Howard).

Hemorrhoids are often unfortunately considered the sole cause of rectal bleeding. They may have preceded the carcinoma and been aggravated by the development of tumor, or they may appear as a consequence of regional interference with the return circulation. *A diagnosis of hemorrhoids alone should not be made in an aged patient without a thorough rectal palpation and proctoscopic examination.*

lar to that of lymphosarcoma elsewhere. It may form a large palpable mass except when it appears in the rectosigmoid region. The patients are often in good general condition and may be without symptoms referable to the large bowel but may have a peripheral lymphadenopathy. Biopsy of one of these nodes reveals a lymphosarcoma. Primary lymphosarcoma of the rectum often shows a polypoid lesion with submucosal nodules. The presence of giant rugae gives the bowel a convoluted appearance (Fig. 421) and an experienced observer may be able to make the diagnosis from the proctoscopic appearance alone (Winkelstein). Roentgenologically the lymphosarcoma often shows intact mucous membrane for the tumor begins in the submucosal lymphatic tissue. Usually there is a large filling defect with smooth margins. Lymphosarcoma may be treated by radical surgical resection or by radiotherapy. The polypoid lesions of the large bowel may be relatively benign in their evolution and in this group local excision may be all that is necessary.



Fig. 421. Lymphosarcoma of the large bowel with prominent giant rugae in convoluted appearance. (Courtesy of Dr. W. H. A. Cameron.)

Melanomas arising from the mucocutaneous junction tend to involve the submucosa of the rectum. It is interesting that these tumors may or may not be black in color and are very frequently polypoid and that even with sessile tumors there is a certain mobility. A healthy mucosa covers the tumor but as the neoplasm grows the mucosa may become superficially ulcerated. Often there are satellite nodules beneath the intact mucosa. They can be located at the anus in the sigmoid or in the ampullary area but are limited to one or only a few. These tumors frequently metastasize bilaterally to the regional nodes. Very frequently the metastases contain numerous subcutaneous nodules which may be within the years of life deeply pigmented. Melanomas of the colorectal region may rarely but often directly invade the adjacent structures but it is difficult to distinguish the extent of the liver metastases.

radiates to the perineum or thigh (particularly in carcinoma of the rectum) usually indicates extension of disease to the pelvic walls and often means nerve invasion

The patient with carcinoma of the large bowel is often dehydrated and anemic and has lowered serum proteins. To counteract these clinical abnormalities before operation, large doses of vitamin C, with blood transfusions and the administration of a high protein diet if necessary, should be given. Prophylactic penicillin materially reduces pulmonary complications. Courses of sulfasuxidine diminish bacterial flora in the large bowel. Cecostomy may have to be done to decompress an obstructed colon.

*Operability at Exploration*—At the time of exploration there may be evidence of distant metastases and the liver may show extensive replacement by carcinoma. Peritoneal implants may be present or the tumor may have metastasized to high nodes along the aorta. These findings usually contraindicate surgery. If the carcinoma is fixed both anteriorly and posteriorly or if the bladder base is involved the operation is of questionable value. At times there are well defined nodules on the surface of the liver which may simulate metastatic carcinoma; it should be emphasized, however, that these may be hemangiomas, lymphangiomas, bile duct adenomas, localized areas of fibrosis, or healed tubercles of the liver. If there is any question of the nodule being benign rather than malignant, there should be no hesitation in completing the surgical procedure. Conversely, Goligher has pointed out that invisible, nonpalpable liver metastases may be present at the time of operation. In thirty-one patients dying a few days postoperatively, the liver was apparently normal, but at autopsy five contained carcinoma within the depth of the liver. Early ambulation after surgery reduces postoperative complications. A Wangensteen suction as a routine for the first two postoperative days is recommended by some surgeons to reduce complications from distention. Continuous spinal anesthesia is the anesthetic of choice. Closure of the abdominal incision with steel wire reduces wound infection and dehiscence.

*Surgical Intervention*—The surgical intervention for carcinoma of the large bowel should effect the *wide removal of the primary tumor with as much of the draining lymph node areas as possible*. As the limits of operability are extended, the operative mortality must increase. Therefore, in evaluating any statistics of carcinoma of the large bowel, the figures of operability and the number of cases of operative mortality should both be reported, for their relationship is obvious. For instance, at the Lahey Clinic in 1941 carcinoma of the colon and rectum had an operability of 81.4 per cent (140 resections). There were seven deaths—an operative mortality of only 5 per cent (Cattell, 1943). The cases seen at our hospital are somewhat more advanced because the patients come from rural areas; there was an operability of 78 per cent in all the patients on whom exploration was carried out, which was 67 per cent of all patients seen. Of the first 220 patients with carcinoma of the colon and rectum, the operation could not be attempted in thirty-one, exploration was carried out on 189 but forty-two of these were found to be inoperable. There were ten palliative resections and

## Treatment

**PREVENTION**—The treatment of polyps of the large bowel is a definite preventive measure. In the *single polyp* with a long pedicle, resection can easily be done through the proctoscope by an electrocautery snare. If the polyp lies above the level of the peritoneal reflection, it should preferably be removed at laparotomy because danger of perforation exists when excision is attempted through the proctoscope. At laparotomy, effective removal is easy, danger of peritonitis is obviated, and it is possible to explore the rest of the bowel for other polyps.

The treatment of congenital *polyposis* of the large bowel must be radical, for given enough time, the disease becomes malignant. Pfeiffer believes that treatment should include fulgurations of all the polypi in the anus, rectum, and sigmoid followed later by ileorectosigmoidostomy and finally by colectomy. This procedure still carries the risk of carcinoma developing in the terminal segment of bowel.

Coller had six patients in whom cancer of the rectum and polyposis were superimposed. He performed total colectomies preceded by combined abdominoperineal resections for the rectal lesions. This seems to be the most logical procedure.

## SURGERY—

**Operability Before Exploration**—The treatment of carcinoma of the large bowel is primarily surgical, but the type of operation depends on the area affected by the tumor. There are several clinical findings which contraindicate exploratory laparotomy: (1) extremely poor general condition of the patient not correctable by strenuous preoperative therapy, (2) serious cardiac conditions including recent coronary disease and aortic valvular disease (in sufficiency or stenosis, but well compensated nonvalvular disease such as hypertensive or arteriosclerotic is not a contraindication to surgery), (3) distant metastases. Peripheral lymph node metastases are infrequent. At times a supraclavicular lymph node is present, and if the tumor involves the mucocutaneous junction, then metastases may be present in inguinal lymph nodes. The abdomen may have a doughy consistency preceding the development of metastases which indicates peritoneal implants. The pathologic proof of such metastatic involvement is however, essential. The suspected node metastases may be aspirated or formally biopsied. Aspiration of liver masses can be done and if ascitic fluid is present, this can be aspirated and its sediment studied for the presence of carcinoma. If there is any question of bone metastases, roentgenograms should be taken, preoperative films of the chest are indicated to rule out pulmonary metastases.

Other relative findings often indicate inoperability, but definite conclusions should not be drawn until exploration is done. In our hospital fixation of the tumor as appreciated at rectal palpation indicated inoperability of two thirds of the cases in the male while fixation in the female meant inoperability in only one third of the cases. If there has been a weight loss of over twenty five pounds hepatic involvement may be found at operation. Pain which

naturally increases the operative mortality Sugarbaker (1946) reported five operative deaths (15 per cent) in the entire group of thirty-four patients, but this added risk is definitely justified by the final results Dixon reported a large series of patients in whom portions of the urinary bladder were resected during radical operations for cancer of the sigmoid or rectosigmoid In sixty-four patients with involvement of the urinary bladder, forty were subjected to radical resection Fifty-nine of these cases occurred in men and five in women There was an immediate operative mortality in seven cases

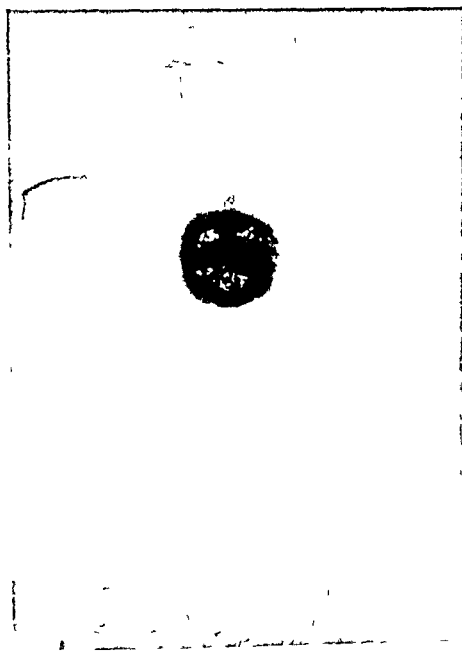


Fig. 424 —A colostomy stoma following abdominoperineal resection No colostomy bag is necessary

*Colostomy and perineal resection* is a compromise procedure, because the regional node areas are not effectively removed This operation is indicated only when there are low-lying lesions for which, because of age and other factors, the combined abdominoperineal resection would result in prohibitive operative mortality The *abdominal resection and colostomy* of Hartmann is also a compromise procedure, for although it effectively removes node-bearing areas, the tumor itself is not widely excised This operation may be necessary in poor-risk patients *Sphincter-saving* operations are resections and anastomoses that appeal to the patient because intestinal evacuation continues normally (Wangensteen, Bacon), but local recurrences and lymph node metastases are obviously greater in number It does not seem reasonable to replace the best procedure (ab-

137 curative resections, and in the latter group thirteen had been explored and considered inoperable elsewhere (Sugarbaker, 1946)

For carcinoma of the rectum ampulla, and low sigmoid, the *abdominoperineal one stage resection* of Miles is the procedure of choice (Fig 423) In this operation the bowel is sectioned well above the tumor and the proximal segment brought out as the permanent colostomy and anchored in the abdominal wall The distal segment is freed The patient is turned over and the specimen removed by excising the anus and bringing out the freed segment of bowel This results in the removal of a considerable length of bowel both above and below the tumor and the operation permits radical removal of lymph node bearing areas This operation is usually applicable to somewhat over 90 per cent of the resectable cases and can be done with an operative mortality of less than 5 per cent The *abdominoperineal two stage resection* (Lahey) is used in the other 10 per cent cases in which there is partial low grade obstruction which cannot be relieved by decompression and sometimes in cases of perforation with extracolonic abscess In this last instance the first stage is carried out with drainage of the abscess followed at an appropriate time interval by the second stage

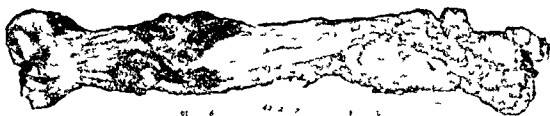


Fig 423—Surgical specimen of an abdominoperineal resection for carcinoma of the rectum The length of bowel removed is justified by the simultaneous resection of lymph node draining areas

*Enlarged operations* may be required in carcinoma of the sigmoid and recto sigmoid because of adherence to or involvement of the bladder prostate vagina, uterus or small bowel In women the bladder is less frequently involved but the vagina and the uterus may be invaded It is not possible to determine at operation whether fixation of the tumor to these organs is neoplastic or inflammatory We have found that a thorough histologic investigation often reveals the presence of carcinoma in the areas of inflammation The prostate however is rarely implicated, for it is well protected by Denonvillier's fascia

The simultaneous resection of a rectal tumor and an invaded uterus was apparently first done by Schwartz (1903) and Goulioud (1908) Albertin (1911) perfected the technique for an abdominoperineal en bloc resection of the entire female pelvic contents, and Chaher (1924) reportedly performed this operation with success In our hospital Bricker performed twenty abdominoperineal resections for carcinoma of the rectosigmoid which included some other structure (uterus bladder prostate small intestine) To this group Sugarbaker added fourteen cases The removal of adjacent organs



Extension of the operation can also be done when a tumor of the colon becomes fixed to the liver, gall bladder, stomach, or anterior abdominal wall. But again, the operative mortality is increased when portions of these organs are removed along with the primary tumor. The operation is justified, however, because carcinoma of the large bowel may locally extend and implicate neighboring organs without giving distant metastases.

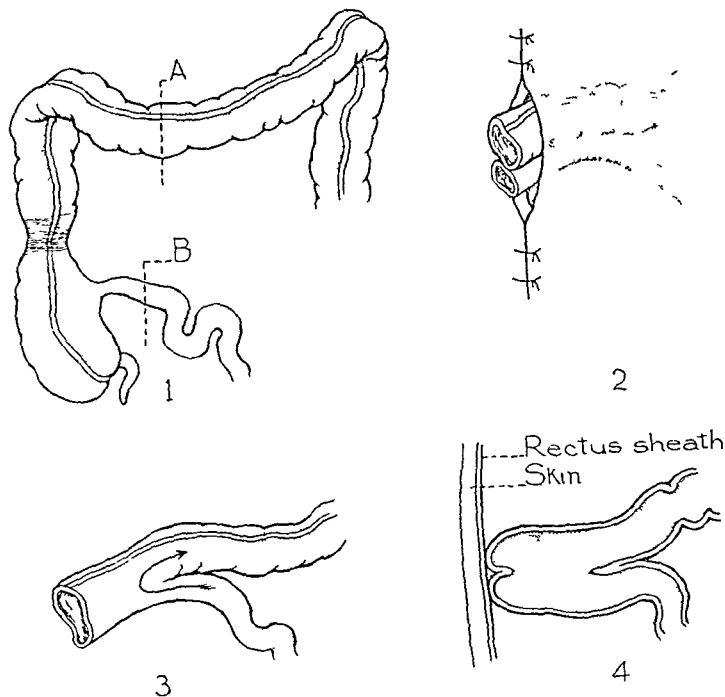


Fig. 425—Schematic representation of the steps necessary in a Mikulicz procedure in which after resection of the tumor loops of bowel are resutured the spur is crushed and bowel continuity re-established.

**RADIOTHERAPY**—Adenocarcinomas of the large bowel may show some radiosensitivity but they are rarely radiocurable, even under ideal conditions (Shedden, Lenz). Treatment by means of interstitial curietherapy leads to radionecrosis and perforation in a large proportion of the cases (Regaud). External roentgentherapy, while offering the advantage of possible protraction and elimination of necrosis, seldom succeeds in sterilizing the tumor locally, and in addition it cannot be expected to irradiate sufficiently the entire lymph-draining area. The relatively good results of surgery even in advanced cases do not justify any attempt to treat these lesions by irradiation.

Roentgentherapy as a preoperative measure has only the value of an anti-inflammatory agent, and it is doubtful whether it really contributes any definite advantage.

dominoperineal resection) with an inferior substitute which gives poorer results. It is somewhat comparable to doing a simple mastectomy with removal of the low axillary lymph nodes for an operable carcinoma of the breast. In certain instances, however, the patient may refuse colostomy, and rather than no treatment at all, a sphincter saving operation may be justified. The patient should be challenged, however, with the alternative of living with a colostomy or dying with a sphincter. It is not necessary for a patient with a colostomy to wear a bag and the patient can be trained to substitute irrigation for defecation (Fig 424). Education concerning colostomy should be thorough and be emphasized during the first six months of postoperative care.

*Palliative resections* for carcinoma of the colon or rectum in the presence of single metastatic nodules in the liver have been done. Cattell reported one patient on whom he had done an abdominoperineal resection plus a resection of a single metastatic nodule. This patient lived twenty two months before dying of recurrence. Even if there are several metastatic nodules in the liver, it might be worth while to remove the primary carcinoma, for some prolongation of life may be obtained and the postoperative survival period is more comfortable. The abdominal resection and colostomy of Hartmann is sometimes used as a palliative procedure in the face of liver metastases.

If the carcinoma is inoperable, then *palliative colostomy* can be done. This procedure is not indicated in the absence of obstruction, however. When obstruction is complete this procedure relieves the obstruction, but the patient continues to have very distressing symptoms with the passage of blood and mucus due to the tumor. It should also be remembered that the operative mortality of this palliative procedure may be as high as 30 per cent.

There are two surgical procedures for the treatment of lesions of the cecum and colon. When there is no obstruction and the bowel is not edematous or distended, and particularly if the lesion is small and early with little chance of having metastasized, the experienced abdominal surgeon can do *primary resection and anastomosis* with a low operative mortality. Zininger (1943) reported forty five cases with only four deaths. This operation is well suited for radical resection of lymph node draining areas. The risk of peritonitis is low. It is also argued that the operation eliminates spur crushing and other annoyances accompanying a colostomy. By contrast, the proponents of the *resection followed by exteriorization* of Mikulicz argue that the increased risk of peritonitis is obviated by this procedure. In the Mikulicz' procedure the tumor is sectioned and removed with lymph node bearing areas. Blind loops of bowel are sutured together and brought out through the abdominal wall as a double barrel colostomy. The spur dividing these two loops prevents communication between the two segments. Later the spur is crushed, the blind loops of bowel turned in and the lumen of the large bowel then becomes continuous (Fig 425). Gordon Taylor performed 138 exteriorization resections for carcinoma of the colon with only seven deaths a mortality of approximately 5 per cent. It is probable that this procedure is preferable when the surgeon only infrequently encounters large bowel surgery.

The type of operation also influences the end results. Naturally if a compromise operation is done the end results are poorer than with radical resection. If it is necessary to remove other organs at the time of abdominoperineal resection for carcinoma of the rectum or upper sigmoid then the prognosis is altered because these cases are much farther advanced. Bricker performed twenty abdominoperineal resections for carcinoma of the rectum and recto-sigmoid at our hospital (1940-1941), including the removal of additional structures (bladder, uterus, prostate, ileum). Five of these twenty patients (25 per cent) were well at the end of five years (Sugarbaker). Of thirty-three patients reported by Dixon surviving radical resection of sigmoid or rectosigmoid with portions of the urinary bladder, twenty had survived for variable periods of time and seven of these had already lived five or more years.

If tumor involves the bladder base then the prognosis is extremely poor. If there is fixation of a carcinoma of the rectum in a male patient the outlook for survival is very much reduced; only one of eleven patients in whom resection was carried out at our hospital survived four years. Fixation in the female is not as significant; in sixteen of our patients seven survived (two for three years, one for four years, and four for five years) (Waggoner). Palliative colostomy for advanced cases does not prolong life and the operative mortality is much greater than with an abdominoperineal resection in operable cases.

The degree of tumor extension has an important bearing on the outlook. Dukes divided his cases into three groups. Group A presented wall involvement but no spread beyond the serosa (Fig. 426). Group B had involvement of the wall and spread beyond the serosa but no regional lymph node involvement, and Group C revealed spread through the wall, involvement of the serosa, and metastases to the regional lymph nodes. Gabriel found that of his patients in Group A 90 per cent survived over five years, of those in Group B 65 per cent lived for five years, and of those in Group C there was only a 20 per cent five year survival. In Gimmell's series, also using Dukes' classification, the patients in Groups A, B, and C had 100, 43, and 23 per cent five year survivals, respectively.

The presence or absence of lymph node metastases is probably the most critical single factor in the prognosis of carcinoma of the large bowel (Table XXI) but further qualifications of node involvement should be made. If the node lies just above the tumor, the prognosis is far better than when the node metastasis has extended up to the point of the ligature (Gordon-Watson). With ligature metastases, tumor is obviously in other locations and the operation is palliative rather than curative. If there is involvement of nodes below the neoplasm, the significance is ominous because this means that all nodes above the tumor have been implicated and that retrograde extension has occurred.

The grading of the tumor is also of prognostic value, three grades being more practical than four. Metastases increase proportionately with the grade. Signet-ring mucinous carcinomas (as contrasted to colloid carcinoma) have a high grade (Gimmell-Raiford). In our hospital they have tended to occur in

# Prognosis

Dalund found that in 100 untreated patients with carcinoma of the rectum the mean duration of life after the diagnosis had been made was fourteen months. Forty five per cent lived less than one year, 75 per cent lived less than two years, and 90 per cent lived less than three years. The location of the lesion has some bearing on prognosis. carcinoma of the right colon has the

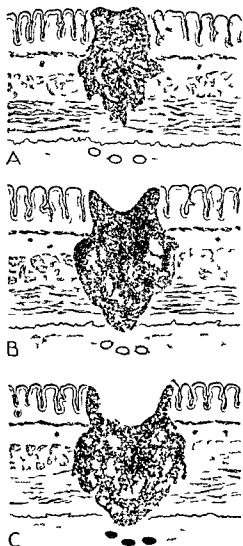


FIG. 47.—Schematic representation of Duke's classification of carcinoma of the large bowel. A represents invasion of the muscle only; B represents invasion to the serosa and C represents invasion through the serosa and involvement of the regional lymph node.

best outlook of all carcinomas of the large bowel, and carcinomas of the rectum as a group have the worst prognosis. The five year survivals found by Dixon were: right colon, 72 per cent; descending colon, 63 per cent; and sigmoid colon, 44 per cent. Cattell (1944) reported that 55 per cent of his patients with carcinoma of the colon showed no evidence of recurrence between five and nine years. Hayden reported a series of ninety eight patients in whom abdominal perimetral resection for carcinoma of the rectum had been done. Thirty two or 33 per cent survived without evidence of disease from five to fourteen years.

In 24 per cent vein invasion was present and yet there was no evidence of lymph node involvement. Very commonly, however, vein invasion accompanies lymph node metastases. Nerve sheath invasion is usually found in advanced cases. In Seefeld's thirty patients with perineural and endoneural sheath involvement, the lymph nodes were also involved in twenty (60 per cent). A goodly proportion of these patients develop local recurrence. As confirmation of the importance of these gross and microscopic findings, Lahey (1945) found in his large series of carcinoma of the rectum that if lymph node involvement and blood vessel invasion were absent and the lesion was limited to the bowel, 90 per cent of the patients survived and were well for five years or more. With lymph node metastases the five-year survival rate was 37 per cent and if other structures were involved, 30 per cent. Blood vessel invasion proved to have a very ominous prognosis for only 14 per cent survived five years.

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TABLE XXI. PROGNOSIS OF CARCINOMA OF LARGE BOWEL ON BASIS OF CLINICAL AND PATHOLOGIC FACTORS

OUTLOOK	CLINICAL FINDINGS		PATHOLOGY	
			GROSS	MICROSCOPIC
Excellent	No symptoms	Tumor movable and small	Polypoid, limited to bowel wall, not circumferential, carcinoma arising in polyp	Type A (Dukes) no metastases, no vein invasion, no perineural sheath invasion, low grade tumors
Fair to good	No symptoms except local weight loss less than 20 pounds, no perineal pain	Tumor fixed or not	Partial circumferential lesion polypoid	No perineural sheath invasion, no vein invasion, type A, B or C (Dukes), no node involvement or only node involvement in the immediate vicinity of tumor
Poor	Weight loss greater than 20 pounds, pain in perineal region and thighs	Tumor fixed	Circumferential lesion—deeply excavating, submucosal extension, vessel invasion, lymph node metastases	Perineural sheath invasion, vessel invasion, lymph node metastases, signet ring type, type B and C (Dukes), high percentage high grade tumors
Hopeless	Distant metastases	Lungs Bone Liver Peritoneal implants Para-aortic lymph nodes Pancreatic Inguinal		

Secondary involvement of contiguous organs does not necessarily give a bad prognosis but does increase operative mortality. The organ involved and the degree of invasion are important. Compromise surgical procedures (sparing operations, perineal resections) may not be the result. The type of spread and percentage of the site on a certain plane of dissection and the ability of the surgeon influence in postoperative mortality.

younger individuals. Carcinomas of the colon are more differentiated than the rectal carcinomas. The degree of invasion is related to the grade. The more undifferentiated the tumor the more invasive it becomes. Most of Grinnell's Grade A cases (Dukes' classification) were Grade I and very few were Grade III. Vein invasion by tumor often means grave consequences. As Brown indicated if at least three sections of the tumor are taken and vein invasion is present, it will invariably be demonstrated microscopically. When this evidence of involvement is found in the surgical specimen and yet no metastases were seen at operation there is still a fair chance that metastases will develop within the liver, long bones or some other organ. Brown found 67 per cent of the patients with intravascular invasion by tumor had visceral metastases.

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## CARCINOMA OF THE ANUS

### Anatomy

The anus, theoretically an orifice, is anatomically a short canal 15 to 20 mm in length which extends from the semilunar valves to the outer surface of the posterior perineum, ending the digestive tract

Most important among the constituents of the anus are its muscular fibers which form the internal and external anal sphincters. Between these sphincters there are ductlike structures which sometimes empty into the fibers of the internal sphincter or into the crypts of Morgagni and that are lined, for the most part, by columnar epithelium which, in the presence of infection, can undergo metaplasia to squamous epithelium. The anus is covered by a stratified squamous epithelium that extends up to the mucocutaneous junction where abrupt transition to columnar epithelium takes place. Externally, the skin of the anus is continuous with the skin of the posterior perineum. The outer anatomic limits of the anus are formed by a circle 6 cm in diameter, centering in the orifice. The skin of the margin of the anus is slightly more pigmented than the surrounding skin and has numerous folds.

**Lymphatics**—The lymphatics of the anus communicate above with those of the rectal ampulla and below with the lymphatics of the perineum (see Lymphatics of the Rectum and of the Penis, pages 577 and 768). Some of the upper lymphatics of the anus may lead directly to the anorectal or the hypogastric lymph nodes (Fig 427). The inferior portion of the anus has a large subdermic network of lymphatics which sweep upward along the inner aspect of the thigh to end in the superficial inguinal lymph nodes (Fig 428).

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## CARCINOMA OF THE ANUS

### Anatomy

The anus, theoretically an orifice, is anatomically a short canal 15 to 20 mm in length which extends from the semilunar valves to the outer surface of the posterior perineum, ending the digestive tract

Most important among the constituents of the anus are its muscular fibers which form the internal and external anal sphincters. Between these sphincters there are ductlike structures which sometimes empty into the fibers of the internal sphincter or into the crypts of Morgagni and that are lined, for the most part, by columnar epithelium which, in the presence of infection, can undergo metaplasia to squamous epithelium. The anus is covered by a stratified squamous epithelium that extends up to the mucocutaneous junction where abrupt transition to columnar epithelium takes place. Externally, the skin of the anus is continuous with the skin of the posterior perineum. The outer anatomic limits of the anus are formed by a circle 6 cm in diameter, centering in the orifice. The skin of the margin of the anus is slightly more pigmented than the surrounding skin and has numerous folds.

**Lymphatics**—The lymphatics of the anus communicate above with those of the rectal ampulla and below with the lymphatics of the perineum (see Lymphatics of the Rectum and of the Penis, pages 577 and 768). Some of the upper lymphatics of the anus may lead directly to the anorectal or the hypogastric lymph nodes (Fig 427). The inferior portion of the anus has a large subdermic network of lymphatics which sweep upward along the inner aspect of the thigh to end in the superficial inguinal lymph nodes (Fig 428).

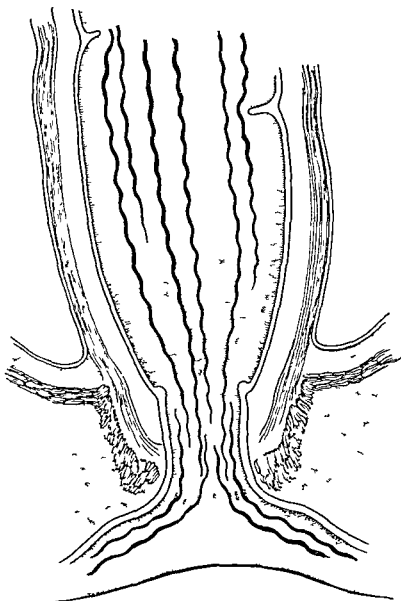


Fig 4\*\*—Schematic drawing of the lymphatics of the anus showing the overlapping of the perineal and rectal lymphatics

### Incidence and Etiology

Carcinomas of the anus are relatively uncommon. When they are included in the same group with carcinomas of the rectum, they make up only about 5 per cent of the entire group. The incidence of carcinoma of the anus is highest in women (about 65 per cent), while carcinoma of the rectum is most frequent in men (60 to 70 per cent). There seems to be some difference in the sex distribution, depending on whether the tumor arises in the perineal or in the rectal aspect of the anus. Gabriel reported twenty-four males in a group of twenty-nine patients with carcinomas arising from the anal margin, while he found twenty-three females in a group of twenty-six patients with carcinomas arising from the anal canal proper. The greatest incidence of carcinoma of the anus is found between 50 and 60 years of age.

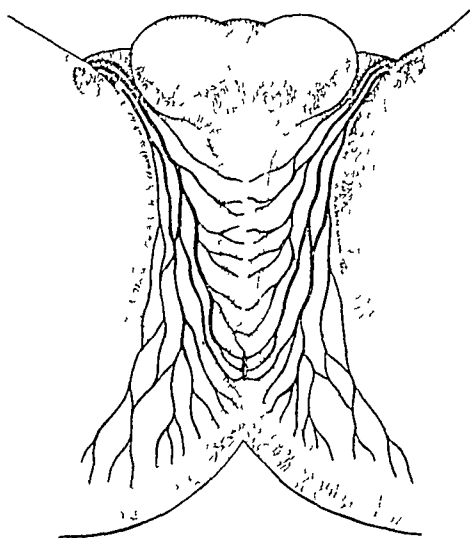


Fig. 128. Schematic drawing of the lymphatics of the anal region which sweep upward to enter in the inguinal lymph nodes.

Pre-existing lesions of the anus have been reported in a great number of patients (Rosset). These pre-existing lesions include anal fistulas, condylomas, and hemorrhoids, but although they might contribute to the development of carcinoma, they cannot always be called precancerous lesions.

### Pathology

**Gross Pathology**—Early carcinoma of the anus is often represented by a small nodule superficially ulcerated, accompanied by evident secondary infection found within the anal margin. Carcinomas arising within the canal are usually exophytic and spread considerably more in surface than do those on the anal margin. Internally the tumor may extend beneath the intact rectal

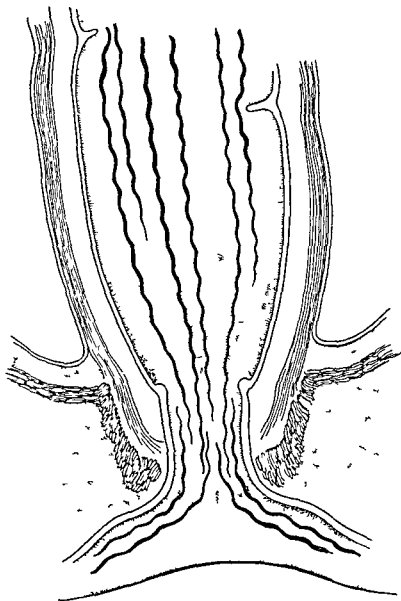


Fig 477—Schematic drawing of the lymphatics of the anus showing the overlapping of the perineal and rectal lymphatics

**Microscopic Pathology**—Most tumors of the anus are epidermoid carcinomas having various degrees of differentiation. Adenocarcinomas are very rare. Those tumors arising externally appear to be more differentiated than those which develop in the anal canal (Gabriel).

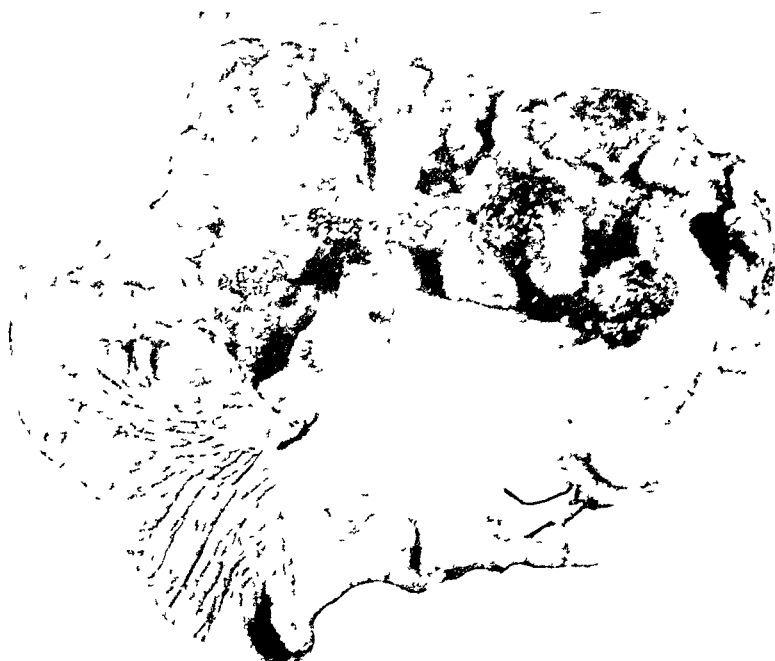


Fig. 431—Primary adenocarcinoma of the rectum with typical burrowing growth retro and invasion and ulceration of the anus.

### Clinical Evolution

Carcinoma of the anus develops unobtrusively and is usually not discovered until a year or eighteen months after onset. One of the first symptoms observed is *pruritus* which may be associated with most of the benign conditions of the anus (condyloma fissures, leucoplakia). As the tumor grows in size, *tenesmus* not relieved by evacuation, may appear. *Pain* and a heavy sensation in the lower rectum not relieved by defecation, may become increasingly noticeable and there may be small repeated rectal hemorrhages.

Common constitutional symptoms such as fever, weight loss, anemia, and asthenia are usually absent unless the lesion is far advanced and is associated with considerable infection or distant metastases. The tumor will present itself in the form of an ulcerating lesion with raised, greatly indurated edges (Fig. 432), or on the contrary in the form of an exophytic rather soft papillary growth extending both on the perineal and the rectal aspects of the anus.

mucosa and become ulcerated further above in the form of an apparently separate rectal tumor (Figs 429 and 430). It is, perhaps interesting to note that carcinomas of the rectum seldom show retrograde submucosal extension to the anus. When carcinoma of the rectum arises near the mucocutaneous junction it not infrequently fungates and ulcerates at the anus (Fig 431). Carcinoma of the anus invades perianal skin, ischioanal fat and muscles of the sphincter rather commonly. Further extension may result in invasion of the levator ani, the coccygeus muscles, the prostate, pelvic peritoneum, base of the bladder, cervix uteri and broad ligaments (Kewes).



Fig 429

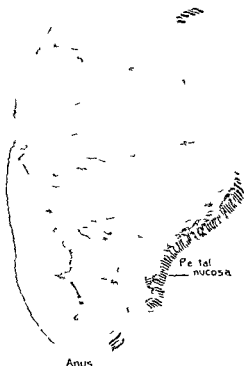


Fig 430

Fig 429—Lilliermoll carcinoma arising at the mucocutaneous junction of the anus presenting a penetrating ulcer in the rectal ampulla. This case was thought to be a primary carcinoma of the rectum.

Fig 430—Schematic representation of submucosal extension of the same lesion with replacement of muscle and ulceration of rectal mucosa.

**Metastatic Spread**—Tumors which develop within the anal canal metastasize via the lymphatics of the rectum to the perirectal nodes while the tumors which develop in the perineal aspect of the anus metastasize to the inguinal lymph nodes.

tion clinically, but this most often occurs in young Negroes who present a positive Fier test. In every case a biopsy should be done in order to eliminate the possibility that an early carcinoma of the anus does exist, though masked by a pre-existing chronic inflammatory lesion.



FIG. 433.—Surgical specimen of a large exuberant condyloma of the anus with a typical mosaic pattern. (Specimen contributed by Dr. Robert A. Moore, Department of Pathology, Washington University School of Medicine, St. Louis, Mo.)

### Treatment

Evaluation of therapy is difficult, for usually the number of cases reported is small, the treatment variable, and the follow-up short (Cattell).

**SurGery**—Surgical treatment, which is advised for carcinoma of the anus, ranges from a simple economical resection without benefit of a colostomy to an abdominoperineal operation (Miles), followed by a bilateral inguinal dissection. Obviously an economical resection is more often followed by local recurrences and has the disadvantage that it does not take care of the internal metastatic implants. An abdominoperineal resection implies an operative mortality of at least 5 per cent and the necessity of a permanent colostomy, but it allows a considerably larger excision of the potentially invaded area and its draining lymph nodes. Bilateral inguinal dissection is indicated following this operation whenever the nodes are enlarged. Some authors advise a prophylactic inguinal dissection in all instances.

**Radiotherapy**—Most attempts to treat anal carcinomas by radiotherapy have been in the form of interstitial curietherapy or radium applications by means of a molded apparatus. These procedures have given variable results with different authors (Regaud, Gabriel, Binkley). They have the advantage of preserving the anal sphincter and eliminating the necessity of a colostomy.

and obstructing the lumen. Often the inguinal lymph nodes will be enlarged only because of secondary infection, but their metastatic involvement is not infrequent.

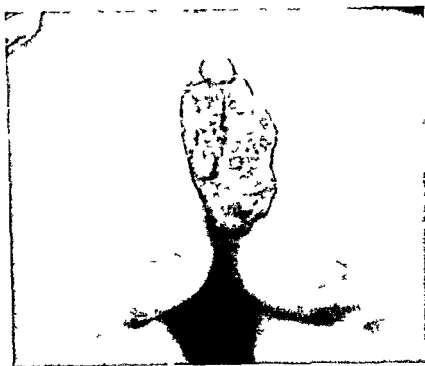


Fig. 432.—Extensive well differentiated epidermoid carcinoma of the anus shown primarily as a perineal growth.

### Diagnosis

**Clinical Examination**—In most cases of carcinoma of the anus the clinical findings are such that the diagnosis may be made on clinical inspection. However biopsy will be necessary to differentiate an epidermoid carcinoma of the anus from an adenocarcinoma of the rectum which has invaded the anus. Moreover examination should include exploration of the rectal ampulla by palpation or by an endoscopy whenever possible in order to establish the upper limits of the tumor. There is of course no possibility of detecting internal metastases. Thorough inguinal palpation should always be done, however for involvement in that region may be discovered, and aspiration biopsy of the inguinal lymph nodes may be useful in resolving uncertainties in diagnosis.

**Differential Diagnosis**—*Melanocarcinomas* which arise in the anus usually give a history of a pre-existing mole and are characteristically pigmented. *Hemorrhoids* which have become thrombosed and indurated may offer difficulty in differential diagnosis but they are rarely ulcerated. *Tuberculous ulcers* are shallow, present soft borders and may be associated with fistulas. They occur most often in young patients who have evidence of tuberculosis elsewhere. *Condyloma acuminatum* which is probably of viral origin may grow very large about the anus (Fig. 433), is rather soft, and microscopically shows localized papillary overgrowth but without invasion of underlying tissue. The *lymphogranuloma venereum* may also offer some difficulty in differentia-



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## CANCER OF THE ACCESSORY ORGANS OF THE DIGESTIVE TRACT

## TUMORS OF THE SALIVARY GLANDS

## Anatomy

The *parotid gland*, so designated because of its relation with the external auditory canal, is the largest of the major salivary glands. It has an irregular form and is found molded around the vertical branch of the mandible. Its borders are in relation with the external acoustic meatus, the sternocleidomastoid muscle, and the mandible. The deep portion of the gland occupies the retromandibular fossa. Its posterior surface is in relation with the sternocleidomastoid muscle, the mastoid process, the posterior belly of the digastric muscle, and the styloid process and muscles. The anterior surface is in relation with the masseter, the mandibular ramus, and the internal pterygoid muscle. Frequently the medial extremity of the gland extends beyond the styloid process and comes in relationship with the carotid sheath and the lateral pharyngeal recess. The entire gland is enclosed in an enveloping sheath of superficial cervical fascia which is attached to the external acoustic meatus, the zygomatic process, and the glenoid fossa. Anteriorly this space is closed by the fused layers of fascia which cover the masseter muscle and join the buccopharyngeal fascia.

The secretion of the parotid gland is gathered through an abundant network of channels emptying into the canal of Stensen, which carries the saliva to the oral cavity. This canal originates in the substance of the gland, follows an upward direction to about 1.5 to 2 cm. from the zygomatic arch, then turns forward and travels horizontally over the external surface of the masseter, perforates the muscle, and opens into the buccal mucosa.

The parotid gland contains in its substance the external carotid artery with its terminal branches, the posterior facial vein, and, lateral to these, the facial nerve and its pes anserina. The facial nerve emerges from the skull through the stylomastoid foramen and immediately enters the substance of the parotid gland. Within the gland the main trunk breaks into two divisions

This advantage alone, however, would not support these procedures if they had not shown some worthwhile results when they were administered by skilled therapists

Röntgentherapy does not seem to have many partisans. This lack of enthusiasm is in part due to the fact that the treatment is often prolonged and it results in uncomfortable perineal reactions. They are, as a general rule, rather radiosensitive epidermoid carcinomas, which, like other such tumors, should benefit by radiotherapy, but the great radiosensitivity of the moist skin of the area requires protraction of the treatment to avoid untoward effects.

The great disadvantage of radiation therapy in the treatment of anal carcinomas is the inability to treat the metastatic nodes which may be present in distant areas. For this reason, radiotherapy, whenever used, should be confined to the treatment of those cases in which the chances of metastases are improbable.

#### Summary of Indications—

*Group I Tumors Restricted to the External Aspect of the Anus Without Involvement of the Rectal Mucosa*—They are usually well differentiated and not likely to present lymph node metastases. This group responds very well to radiotherapy. Prophylactic groin dissection does not seem to be justified because of the infrequent occurrence of metastases.

*Group II Tumors Which Invade the Rectal Mucosa and Which Are Likely to be Accompanied by Pelvic Metastases*—In these cases an abdominoperineal resection of the rectum and anus gives the patient the best chances of a permanent cure. If the tumor is moderately undifferentiated as is commonly the case in this area, the Miles resection should be followed by a bilateral groin dissection. If the tumor is a differentiated one, dissection should be carried out only if the nodes are clinically or pathologically proved.

*Group III Extensive Inoperable Tumors*—These lesions, because of obstruction, may require colostomy and relief of symptoms by means of roentgentherapy.

#### Prognosis

The prognosis of epidermoid carcinomas of the anus depends on several factors. In the first place the degree of differentiation of the tumor will definitely be related to its ability to metastasize. Those tumors which are highly differentiated infrequently present metastases and will have the most favorable prognosis provided that the treatment given, whether it is radiotherapeutic or surgical, is adequate. Less differentiated carcinomas of the anus do not have such a favorable prognosis but may be controlled by a radical surgical excision. In such cases the prognosis will be clarified by thorough study of the surgical specimen and meticulous investigation of the muscle and lymph node involvement. It is believed that a prophylactic bilateral inguinal dissection should increase the chances of survival of patients with undifferentiated tumors. Advanced cases already presenting large inguinal masses are hopeless.

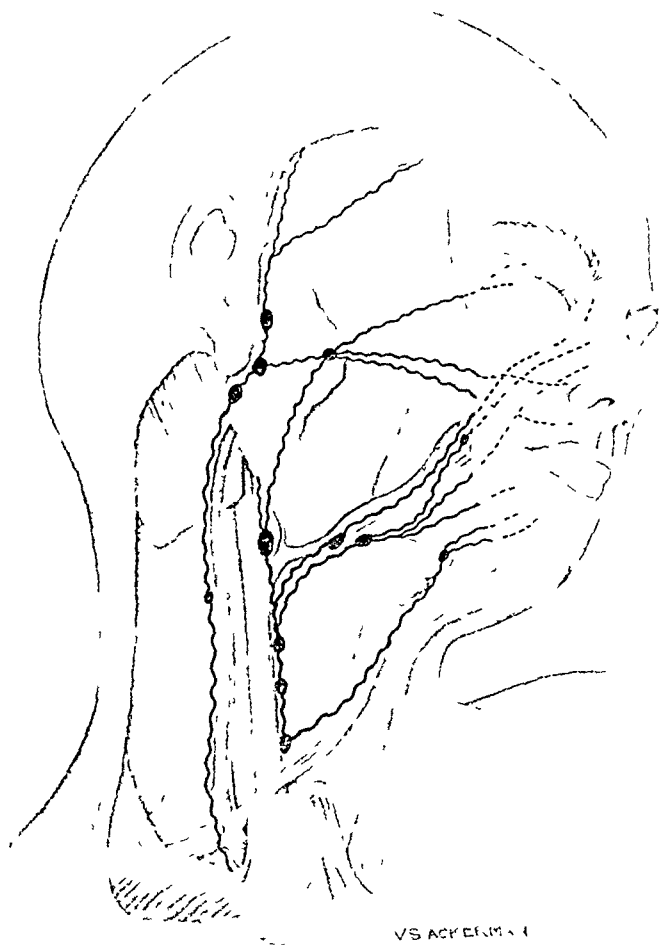


Fig. 435—Schematic representation of lymphatic drainage to the lymph nodes within the parotid and to those in the region of the submaxillary gland. Second relays from this area lead to nodes in the anterior jugular and spinal chains.

the temporo-cervical and the cervicofacial. McCormack found that the point of bifurcation of the facial nerve lies posteriorly and slightly medial to the ascending ramus of the mandible two thirds of the distance between the angle of the mandible and the condyloid process. Variations of facial nerve branching and anastomosis are common.

The *submaxillary gland* is about one fourth the size of the parotid gland. It extends from the lower border of the mandible to the hyoid bone. It is also in relation with the posterior belly of the digastric muscle, the stylohyoid muscle and the mylohyoid muscle. The secretion of the submaxillary gland is canalized by the canal of Wharton which after traveling for 4 to 5 cm opens on the anterior midline of the floor of the mouth.

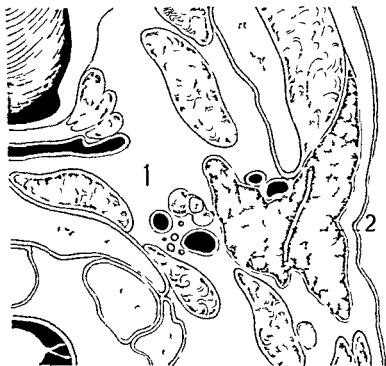


FIG. 434.—Anatomical sketch of a transverse section of the parotid to illustrate its pharyngeal prolongation and its relationship to the first four cranial nerves and \* the approximate level at which the parotid is crossed by the facial nerve.

The *sublingual gland* is one third the size of the submaxillary gland and consequently less than one tenth the size of the parotid gland. It is 2 to 3 cm in length and is 2 cm thick. It is found in the floor of the mouth immediately beneath the mucosa. The sublingual gland is in relation with the medial aspect of the mandible the mylohyoid and the hyoglossus and genioglossus muscles. It is enclosed in a distinct fascial covering and is in intimate relationship medially with the duct of the submaxillary gland. The secretion of the sublingual gland is canalized by a thin duct which opens in the floor of the mouth next to and sometimes into the duct of the submaxillary gland.

**Lymphatics**—The salivary glands have a large interlobular network of lymphatics anastomosing in the form of plexuses and following the direction of the blood vessels and ducts. The lymphatics of the *parotid gland* end in

salivary glands This figure is disproportionately high because so many malignant tumors are referred to the Radiumhemmet The true proportion is probably nearer that of Stein and Geschickter, who reported forty-two malignant tumors (17 per cent) in a total of 241 cases

TABLE XXII ANATOMIC DISTRIBUTION OF 392 MUCOUS AND SALIVARY GLAND TUMORS  
(From Stout, A P Texas State J Med, 1946)

Salivary glands (parotid, 227, submaxillary, 37, sublingual, 1)	265
Palate	64
Lips (upper 16, lower, 2)	18
Rest of oral cavity and pharynx	11
Nasal fossa, sinuses, and nasopharynx	7
Bronchus	1
Lacrimal gland	6
Head and neck	16
Other regions	4

There are a few benign tumors of the salivary glands which need some special consideration The true *adenomas* are rare (Ackerman), most of them in reality are mixed tumors (McFarland, 1927) The *cystadenoma lymphomatosum*, a rare salivary gland tumor, invariably arises from the parotid gland, is encapsulated, varies between 1 and 6 cm, and usually involves the parotid substance for a short distance On section it is soft and fluctuant and the surface usually reveals poorly defined lobules and small cysts lined by papilliferous projections (Martin)

The typical benign mixed tumor varies in size, depending upon the duration of the disease It may exceptionally reach huge dimensions (Fig 456) It is firm, resilient, and not infrequently cystic Differences in consistency are due to connective tissue and cartilage content On section it has a definite connective tissue capsule, and the surface of the tumor not infrequently presents a variegated appearance There may be myxoid areas, zones suggesting cartilage, cystic changes (Fig 437), and gray zones of connective tissue proliferation It is not infrequent for small burgeoning nodules to extend out from the capsule, but they, too, are surrounded by a definite capsule The tumor is usually attached to and intimately associated with the gland, but invariably portions of normal gland remain for identification

The malignant salivary gland tumor is usually much smaller than the benign variant, its consistency depends on its cellularity and the amount of connective tissue The tumors which are predominantly made up of connective tissue cut with increased resistance and obliterate the normal architecture of the gland They grow into the skin and insinuate themselves in the interstices of the surrounding tissue where they speedily become fixed to bone Those in the submaxillary area may invade the mandible and grow into the surrounding muscles (Fig 440) Not infrequently malignant tumors of the parotid cause thrombosis of the external jugular vein and compression of the external carotid artery The more cellular tumor is softer and cystic and may exist for a time within the substance of the parotid, but with increased growth it will ulcerate through the skin and form a voluminous mass which is ulcerating, vegetating, and foul smelling It is prone to hem

the lymph nodes found within the substance of the gland, and frequently also a collecting trunk of lymphatics follows a downward and forward direction and empties in one of the retrovascular submaxillary lymph nodes

The lymphatics of the *submaxillary gland* gather into one or two trunks which are drained by one of the prevascular submaxillary lymph nodes. Some of the deep lymphatics of the submaxillary gland gather into a collecting trunk which follows the facial artery and ends in one of the subdigastric nodes of the anterior jugular chain

The lymphatics of the *sublingual gland* are divided into (1) those which are drained by submaxillary lymph nodes and (2) those which follow in a posterior direction have a long trajectory and finally end in the deep nodes of the internal jugular chain between the digastric and omohyoid muscles. Very rarely the lymphatics of the sublingual gland may be emptied by submental lymph nodes (Rouviere)

### Incidence and Etiology

Salivary gland tumors are rare. McFarland was able to find only about 400 of these tumors over a period of twenty five years in most of the hospitals in Philadelphia. Tumors of the major salivary glands should be classified with similar tumors originating from the mucous glands of the upper respiratory and oral mucosa and also from the lacrimal glands (Figs 451 and 452). In 23700 patients with tumors or tumorlike conditions examined at the Radiumhemmet between 1921 and 1932 276 (1.2 per cent) had tumors of mucous and salivary gland origin (Ahlbom). The average age upon admission for 130 patients with benign and semimalignant tumors was 43 years and for 124 with malignant tumors it was 52 years. There was no difference in the sex incidence in the malignant group but in the benign group there was a definite preponderance of women.

Steiner reports the experimental production of tumors of the salivary gland in rats and guinea pigs by the use of carcinogenic hydrocarbons. Trauma, mumps and infection do not cause salivary gland tumors.

### Pathology

**Gross Pathology**—The major mucous and salivary gland tumors are for the most part found in salivary glands. They are also found in many other locations such as buccal mucosa, base of the tongue, hard palate, soft palate, alveolar ridge, floor of the mouth, pharynx, sinuses, trachea, lip and bronchi. From these areas mixed tumors can arise which do not differ from those arising in the parotid or submaxillary gland. Stout collected 227 tumors of the parotid, thirty seven of the submaxillary and only one of the sublingual gland (Table XXII). The parotid gland was by far the most commonly affected in a ratio of about 14 to 1 in Ahlbom's series. McFarland had 350 parotid and twelve submaxillary tumors in his series. Smith (1939) was able to collect only eleven primary tumors of the sublingual gland. The benign mixed tumors outnumber the malignant mixed tumors. Ahlbom had eighty two instances (42 per cent) of definite malignancy in 193 tumors of the major

follow-up was continued from the initial symptom to necropsy twenty-four (50 per cent) had lymph node metastases these metastases were mainly in the submaxillary lymph node areas the parotid region the parotid triangle, the supraclavicular region, and at times the mediastinum The malignant parotid gland tumors metastasize first to a node intimately associated with the parotid and then involve cervical and supraclavicular groups The nodes usually first



Fig. 438

Fig. 439

FIG. 438—Semimalignant mucoepidermoid type of tumor of the parotid gland. The lesion recurred within a year of surgical excision.

FIG. 439—Semimalignant mucoepidermoid tumor illustrated in Fig. 438. The tumor is grayish white and fairly homogeneous with areas of mucinous changes.

involved from the malignant submaxillary neoplasm are those in closest relation to the gland and are often confused with the primary tumor. The submental and carotid lymph nodes are invaded somewhat later. Lung metastases are not too rare and they may be extensive in spite of absence of clinical signs or symptoms. The very undifferentiated carcinomas, the malignant type of mucoepidermoid carcinoma, and the cylindromatous variety which is some

orrhage and spontaneous necrosis. It speedily invades the sternocleidomastoid, masseter, temporal, and pterygoid muscles. It is not infrequent for the temporomaxillary articulation to be invaded early. The superficial cervical plexus on the external surface of the sternocleidomastoid muscle can be surrounded and compressed. The malignant submaxillary gland tumors extend first to the cellular tissue and the neighboring muscles, including the digastric, mylohyoid, and even sternocleidomastoid. The hypoglossal and the superior branches of the superior cervical plexus may be surrounded. Extension along the internal prolongation of the submaxillary gland to the sublingual gland can occur. The tumor may become adherent to the mandible and rather exceptionally invade it (Fig 440).



Fig 436

Fig 436—Benign mixed tumor of the parotid gland of several years' duration.



Fig 437

Fig 437—Surgical specimen of the same tumor as shown in Fig 436, presenting large area of central cystic degeneration. Note that the tumor is enclosed in a fairly well defined capsule.

**METASTATIC SPREAD**—It is usually reported that metastases of salivary gland tumors are rare, and there is no doubt that the malignant variant of the mixed tumor is much less malignant than malignant tumors in general. However, if these malignant tumors are followed long enough, they rather often develop lymph node metastases. Of eighty-two patients with malignant mixed tumors reported on by Ahlbom, sixteen (20 per cent) had lymph node metastases on admission. Later, over a period of several years, an additional eleven patients developed metastases to lymph nodes, making a total of twenty-seven (33 per cent). Ahlbom emphasized that of forty-nine patients on whom



types designated as an adenocarcinoma are the ones which most frequently metastasize. The last type is particularly prone to give pulmonary metastases. General metastases and in particular bone involvement are not too rarely reported. Malignant.

**Microscopic Pathology**—The classification of salivary gland tumors is confusing. The usual conception of the salivary gland is a tumor in which the benign variety is less benign than the usual benign tumor and the malignant variety is less malignant than the usual malignant tumor. There is no sharp dividing line between the benign and malignant variants. There is an intermediate group in which the tumor is not outspokenly malignant and neither is it very benign. It may eventually metastasize to distant organs. However, in this case the long period in the evolution may take several years. There are also numerous epitheliomas appended to the same type of tumor which makes the classification difficult even for a pathologist. It is therefore thought worthwhile to state a tentative classification of the salivary gland tumors.

#### TUMORS OF THE SALIVARY GLAND

- I Benign tumors
  - A Tumor arising from blood vessels
  - B Lymphangioma arising from lymphatics
  - C Lipoma arising from fat
  - D Adenoma arising from salivary gland
  - E Papillary cystadenoma lymphomatosa
  - F Tumor arising from connective tissue (sarcoma and carcinoma)
  - G Myxoma, etc.
- II Slowly growing or low malignancy
  - A Myxocarcinoma
  - F Adenocarcinoma (adenoma basal cell)
- III Highly malignant
  - A Epidermoid carcinoma
  - B Unresectable carcinoma
- IV Sarcomas

**Benign Tumors**—The *hemangioma* is found most frequently in the parotid region, probably rarely arises from the salivary gland itself and undoubtedly comes from subcutaneous blood vessels. The *lymphangioma* is rarely observed. *Lipomas* arise from fatty tissue in the region of the parotid gland and do not differ from lipomas found elsewhere. True *adenomas* of the salivary glands are very rare, arise probably in many instances from duct epithelium and are composed microscopically of the same type of cell. The oncocytoma (an adenoma) has a dense capsule and once removed rarely recurs. The *papillary cystadenoma lymphomatosa* arising from the parotid salivary gland has a debatable histogenesis. Krausl believes that it arises from a dilatation and proliferation of the orbital inclusion or that areas of salivary gland tissue may become enclosed in parotid and preparotid lymph nodes during glandular development. Martin feels that it arises from heterotopic rests. Microscopically these cystadenomas have a characteristic appearance which can be

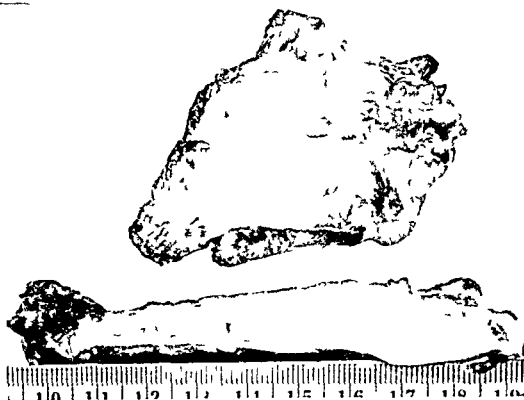


Fig. 440.—Semimalignant cylindromatous tumor of seven years duration arising from the submaxillary gland and directly invading the mandible



Fig. 441.—Metastatic carcinoma in the submaxillary lymph nodes simulating the appearance of a tumor of the submaxillary gland. The primary lesion however had been excised from the buccal mucosa five years previously

easily recognized. They are composed of two elements, epithelial and lymphoid, intimately associated (Fig. 442). These papillary epithelial structures are embedded in lymphoid stroma which may contain germinal centers. The projections are lined by tall, nonciliated, eosinophilic epithelium.

The *true mixed tumors* are complex in nature, but majority opinion holds that they are entirely epithelial in origin (Dunet). Ahlborn believes that they

FIG. 441



Fig. 445

Fig. 444—Photomicrograph of a typical mixed tumor with well-differentiated glands in a dense hyalinized stroma (moderate enlargement).

Fig. 445—Photomicrograph of a recurrent typical mixed tumor. This exactly resembled the primary tumor (moderate enlargement).

Fig 442



Fig 443

Fig 44 —Photomicrograph of a papillary cystadenoma lymphomatosum demonstrating the intimate association of lymphoid and epithelial elements (low power enlargement)

Fig 443 —Typical mixed tumor of the salivary glands presenting cartilage loose fibrous tissue and glands (moderate enlargement)

Fig. 417

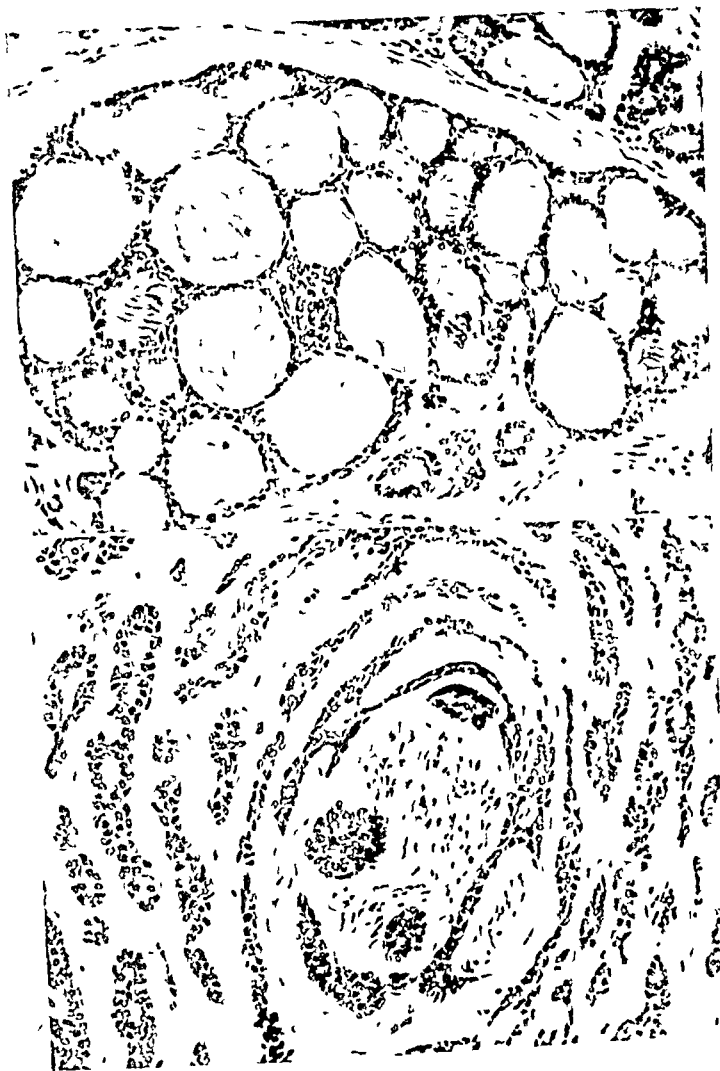


Fig. 118

Fig. 117—Cylindromatous semimalignant salivary gland tumor with overproduction of mucin. Note resemblance to cystic type of basal-cell carcinoma.

Fig. 118—Perineural sheath invasion of a cylindromatous type of salivary gland tumor (moderate enlargement).

arise from the epithelium of adult excretory ducts, acini, and, perhaps at times from detached embryonal epithelial anlage. Recently, Hellwig has produced evidence that they are derived from misplaced elements of the notochord on the basis of embryologic, histologic, and topographic studies. The *typical mixed tumor* is the most common tumor of the salivary glands, and names given to it have depended either upon the predominant tissue or on the basis of each tissue present, so that designations such as fibroepithelioma, fibromyxoma, chondroma, etc., have been used. The cartilage which is present (Fig. 443) indicates that the tumor is quite slowly growing, 55 per cent of Ahlbom's mixed tumors contained cartilage, while only one ninth of the malignant tumors demonstrated its presence. It is not infrequent for these tumors to show small nests of cells within the capsule, and it is not rare for small strands of tumor to form satellite nodules close to the main mass which may not be discovered until surgical excision.



Fig. 446.—Mucoepidermoid, semimalignant salivary gland tumor presenting squamous elements and cells producing mucin (moderate enlargement).

*Semimalignant Tumors*—The *mucoepidermoid* variant recently described by Looe and Becker makes up approximately 5 per cent of the entire group of mixed tumors. It has a characteristic histologic structure and apparently arises from duct epithelium. It is composed of two elements: squamous cells and tumor cells producing mucin (Figs. 439 and 446). Because of the production of mucin, cystic areas may occur. The mucoepidermoid variant does not grow, as a rule, much larger than 4 cm., but it can become definitely malignant and in its malignant variant it is more cellular and may break through its capsule and invade contiguous structures. The *adenocarcinoma* often designated as *cylindroma*, *cylindroma* type, or *basal cell carcinoma* with hyaline stroma makes up 10 to 20 per cent of the salivary gland tumors of

the parotid and submaxillary gland. Microscopically its appearance is characteristic with glandlike structures superficially resembling the cystic type of basal-cell carcinoma and often containing small amounts of mucus within its center (Fig 447). It is often associated with hyaline stroma but never with cartilage. This tumor is much more malignant than is generally suspected, and microscopically it very frequently gives rise to perineural sheath involvement (Fig 448) (Quattlebaum). Such nerve involvement probably accounts for the high percentage of facial paralysis seen in this group.

*Highly Malignant Tumors*—The *epidermoid* carcinoma is one of the most malignant tumors of the salivary gland, although fortunately rare. It grows rapidly and is fairly undifferentiated (Fig 449). It is often associated with considerable infection. It should be emphasized that there are malignant salivary gland tumors which, because of their undifferentiation and rapid growth, are impossible to classify, even with the most meticulous histologic study.

*Sarcomas*—Sarcomas of the parotid gland are extremely infrequent. It is interesting that in analyzing the literature, the percentage of sarcomas in each given series drops precipitously as the pathologic study becomes more critical. Most reported sarcomas of the salivary glands are actually highly malignant tumors of epithelial origin (Fig 450). It is interesting that Stout and Dunet reported no sarcomas in their large series.

*Recurrence of Salivary Gland Tumors*—The recurrence of mixed tumors is one of their most common and disconcerting characteristics. Such recurrences frequently take many years and may be the result of several factors. There is no doubt that many salivary gland tumors have inconspicuous satellite tumor nodules near by. At the time of operation, particularly in the region of the parotid, the surgeon, anxious to conserve the facial nerve, may cut through a small strand of tumor, leaving a nodule to develop slowly and make itself clinically apparent, usually after a long period of time. It is also possible that multicentric origin in some instances is the cause of recurrences. If the tumor is shelled out of its capsule, small persisting bits of tumor may remain within that capsule. Recurrences may also appear in the operative scar or in the region of the prolongations of the parotid gland (pharyngeal or masseter). They may also appear in the carotid region due to tumor within lymph nodes. In the region of the submaxillary gland, where complete surgical removal of the entire gland is possible without disfigurement, recurrences are rare when the operation is radical. A recurrence usually has an evolution more rapid than that of the primary tumor. If facial paralysis appears a month or so after the removal of a tumor of the parotid gland, it is probably the result of recurrence. The microscopic appearance of even the fifth or sixth recurrence with very few exceptions is monotonously similar to the primary tumor (Fig 445). In a few instances the recurrent tumor becomes rapidly invasive and takes on very malignant characteristics, but the original neoplasm in these instances is usually one of doubtful malignancy.

### Clinical Evolution

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age seven years) The first symptom in practically all cases is a small, painless lump which almost imperceptibly increases in size If it is in the region of the submaxillary gland it is often dismissed as an inflammatory lesion of a regional lymph node However with increase in size there is unsightly facial asymmetry and pain The tumors of the region of the parotid gland usually extend downward and appear as lobulated masses on the lateral surface of the neck If there is retroauricular involvement of the parotid by tumor (Fig 453) there may be eversion of the lobe of the ear (Lederman)

Fig 451

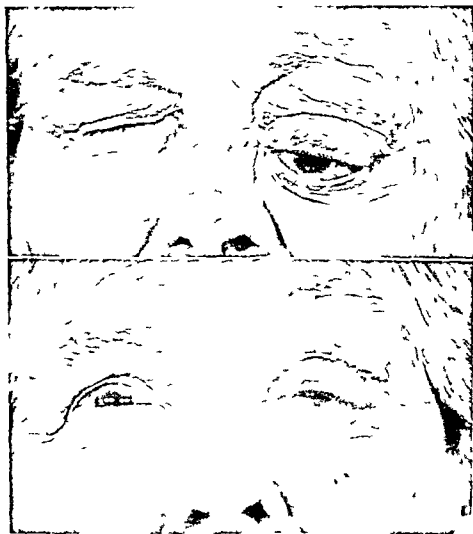


Fig 452

Fig 451.—Mucous and salivary gland tumor (benign variety) arising from the lacrimal gland with exophthalmos and displacement of the eye due to the tumor

Fig 452.—Same patient as shown in Fig 451 following surgical excision of the tumor

The benign mixed tumor, whether it arises from the parotid or submaxillary gland is only rarely the cause of death The huge tumors of the parotid region with pharyngeal extension cause difficulty in mastication and deglutition With inadequate surgery the tumors may eventually become malignant and be the cause of death

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Fig 451

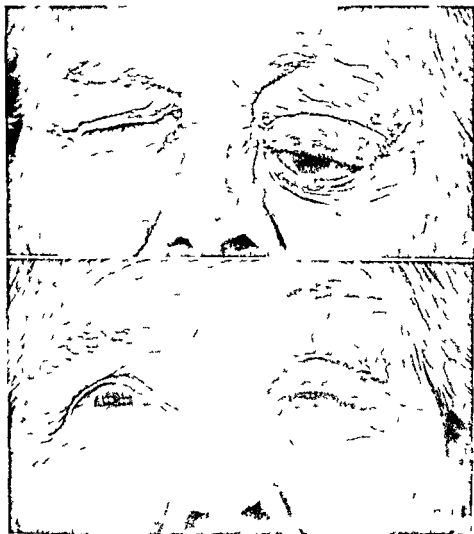


Fig 452

Fig 451—Mucous and salivary gland tumor (benign variety) arising from the lacrimal gland with exophthalmos and displacement of the eye due to the tumor

Fig 452—Same patient as shown in Fig 451 following surgical excision of the tumor

The benign mixed tumor whether it arises from the parotid or submaxillary gland, is only rarely the cause of death The huge tumors of the parotid region with pharyngeal extension cause difficulty in mastication and deglutition With inadequate surgery the tumors may eventually become malignant and be the cause of death

The malignant tumor of the salivary gland grows much more rapidly than the benign tumor, evolution before examination is usually measured in months rather than in years. The first sign of malignant carcinoma of the parotid may be the presence of a small nodule or zone of irregular induration located just in front of the tragus or slightly below or above the angle of the mandible. The skin becomes adherent to the subjacent tumor and becomes depressed. It frequently causes *pain* if the tumor is in the region of the parotid gland, the pain is produced by involvement of one or more branches of the facial nerve. This pain may radiate down the branches of the involved facial nerve.

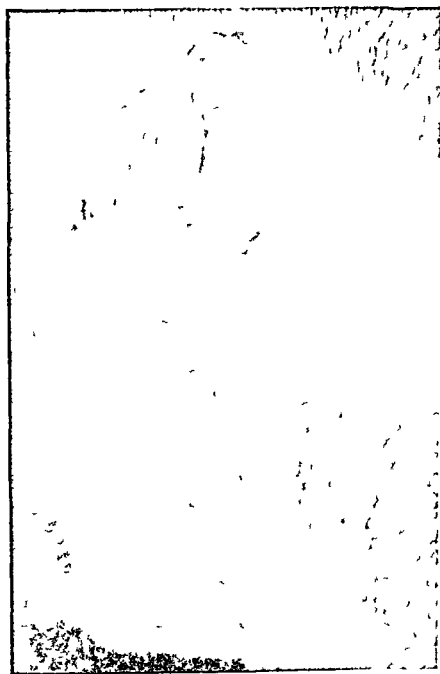


Fig. 453.—Typical early benign salivary gland tumor of the parotid gland with eversion of the lobule of the ear.

Rarely the tumors in the region of the parotid gland may invade the base of the skull to give intractable pain and paralyses of various cranial nerves. The tumor producing large amounts of connective tissue quickly causes retraction of the skin and fixation of deep structures with increasing pain and it seldom ulcerates. Infiltration of the skin often forms a veritable collar of iron (Fig. 457) which may immobilize the head in an attitude of torticollis. The softer tumors grow even more rapidly, tend to give facial paralysis earlier, and are frequently accompanied by severe pain. They may quickly erupt through the skin, ulcerate, hemorrhage, and give rise to foul discharge.

age seven years). The first symptom in practically all cases is a small painless lump which almost imperceptibly increases in size. If it is in the region of the submaxillary gland it is often dismissed as an inflammatory lesion of a regional lymph node. However with increase in size there is unsightly facial asymmetry and pain. The tumors of the region of the parotid gland usually extend downward and appear as lobulate masses on the lateral surface of the neck. If there is retroauricular involvement of the parotid by tumor (Fig. 45) there may be overgrowth of the lobe of the ear. (Lehmann

Fig. 4

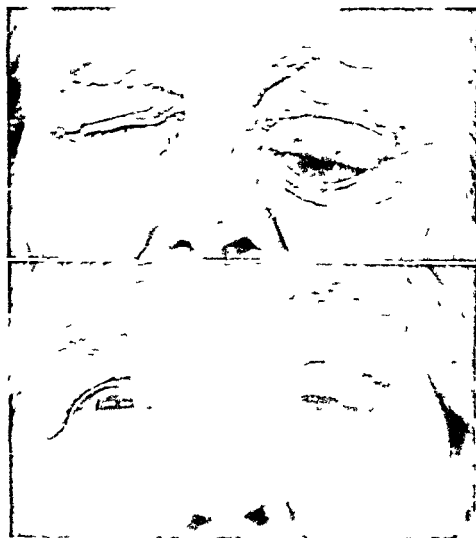


Fig. 4

The large, fixed tumor, extending upward from the parotid gland, is clearly visible in the upper panel. The lower panel shows the same patient from the opposite side, with the tumor extending downward from the parotid gland.

The large, fixed tumor, extending upward from the parotid gland, is clearly visible in the upper panel. The lower panel shows the same patient from the opposite side, with the tumor extending downward from the parotid gland. While the tumor is large, it is not yet large enough to cause the face to be deformed.

If a malignant tumor of the parotid arises from the masseteric prolongation, the tumor may present itself as a lesion of the cheek, and if it infiltrates the masseter or pterygoid muscles or involves the articulation of the temporo maxillary region, trismus may appear. It also may extend from this location in a retrograde fashion to involve the facial nerve and to be associated with facial paralysis and typical metastatic adenopathy. The tumor may also arise in the pharyngeal prolongation and thus the tumor will bulge into the pharynx. The first symptoms may be profound pain radiating to the neck and ear and often there is dysphagia, dysphonia and dyspnea.



Fig. 156—Large parotid gland tumor of twenty-four years duration which recurred several times following inadequate excisions. Patient remains well seventeen years after wide excision and postoperative radiotherapy. (From Desplagne J and del Rucato J A. Bol. Liga contra el cancer. 1930.)

The presence or absence of partial or complete *paralysis* of the facial nerve is an important factor which must be carefully noted in all tumors of the parotid gland. It is relatively rare for the benign mixed tumor to cause paralysis by compression of the nerve (Fig. 454). Only 2 of 104 patients with benign or semimalignant tumors developed facial nerve paralysis (Ahlbom). It is present in about one third of the malignant tumors but may not occur in the carcinomas originating deep within the gland or in its inferior pole. The paralysis is peripheral in type. Early paralysis may be localized to only one of the two branches (the temporocervical and cervicofacial), but as the tumor grows, the paralysis becomes complete. It is usually due to perineural sheath involvement, but in certain instances compression alone may cause these changes. After operation, when the paralysis is due to compression



Fig. 3. Typical benign (xanthoparotoma) of the parotid gland. In this case the tumor was 10 cm in diameter. The patient had no pain.



Fig. 4. Lateral view of a large cystic mixed tumor of the parotid gland.



weight loss. If the tumor arises in the region of the parotid, it may ulcerate through the external jugular, and, on rare occasions, even ulcerate into the external carotid artery and cause hemorrhages. Not infrequently, broncho pneumonia may occur as a terminal event.

### Diagnosis

**Clinical Examination**—The clinical diagnosis of a typical benign salivary gland tumor is not difficult. The tumors of the parotid gland are not attached to the skin or underlying structures and often have a somewhat bosselated surface and a variable consistency, depending upon their cellular make-up (Figs 436 and 453). These benign mixed tumors are usually nontender, firm, and somewhat resilient. The tumors in the region of the submaxillary gland have similar physical signs.

In examining tumors of the submaxillary gland, it is valuable to do a bimanual examination with one hand on the gland and the other within the mouth. If a mixed tumor of this region does not grow toward the buccal cavity, the floor of the mouth is free and nonelevated. With continued growth, the tumor increasingly elongates the gland of the mylohyoid.

At times it may be difficult to determine whether the tumor arises within the anteriorinferior portion of the parotid or in the submaxillary gland. This is of practical importance, for it may determine whether operation will necessitate excision of portions of the facial nerve. If this differentiation is kept in mind, the point of origin is usually resolved at the time of operation. Bimanual palpation with one finger in the mouth and the free hand on the external surface of the tumor also may be helpful in establishing the point of origin. The buccal prolongation of the parotid is behind and above the orifice of the parotid duct, and by buccal palpation, association with the anterior border of the parotid gland can easily be demonstrated.

It is only when a salivary gland tumor has an unusual onset that the diagnosis becomes difficult. A small, inconspicuous, soft, rapidly growing malignant tumor of the parotid gland may have its onset with facial paralysis. The first sign may be enlarged lymph nodes in the neck. The mixed tumor of the parotid may also arise from the masseteric prolongation in which the tumor is exposed as a lesion of the cheek. Its origin is frequently resolved by intraoral palpation and pharyngoscopy.

The malignant salivary gland tumors, particularly in the region of the parotid gland, vary considerably in their clinical manifestations. The tumor may give the impression of an inflammation in a lymph node or a chronic inflammatory lesion of the parotid gland. Later in their evolution the rapidly growing malignant tumors of the parotid gland reveal a friable, vegetating, hemorrhagic growth. In malignant tumors of the parotid, the upper cervical and supraclavicular zones should be investigated. The nodes intimately associated with the parotid gland may be difficult to distinguish clinically (Fig 438). Examination of the regional nodes in submaxillary gland tumors should include those in close proximity to the gland, the upper cervical and even supraclavicular nodes.

alone, facial paralysis may partially or completely disappear and conversely may come into existence postoperatively from edema surrounding the nerve and then quickly subside. Complete facial paralysis may also result from purposely sacrificing the nerve at the time of operation. If a malignant tumor of the parotid arises in the retroparotidian space a syndrome characterized by paralysis of the ninth tenth eleventh twelfth and sympathetic nerves may appear. The symptoms and signs due to this involvement in the retroparotidian space have been dealt with in the section on cancer of the nasopharynx. It is also not rare to find cutaneous anesthesia in the juxtaparotid region due to the destruction of superficial cutaneous nerve filaments.



Fig 4S

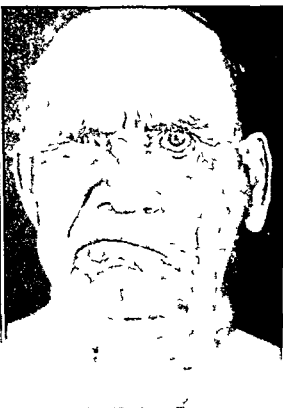


Fig 4S

Fig 4S—Postoperative recurrence of a malignant tumor of the parotid gland firmly fixed to underlying structures. Skin is attached and the tumor surrounds the neck as a collar of iron.

Fig 4S—Same patient as shown in Fig 4S showing typical peripheral type of facial paralysis.

Malignant submandibular gland tumors can invade the periosteum or break into the cavity of the mandible where they may compress or invade the dental nerve and cause pain referred along the jaw to the region of the ear and temple.

The malignant tumor of the salivary gland in its rapid growth and extension may metastasize to the regional nodes and infrequently to lungs bones and other distant organs. Usually however death is caused by a number of factors. The tumor may ulcerate through the surface and become infected. This in turn results in secondary bacteremia sepsis and subsequent

parotid gland and the ordinary benign mixed tumors are usually easily diagnosed. Any unusual variation of either the benign or malignant tumor may be extremely difficult to interpret, and an incisional biopsy may have to be done. At the time of operation, a frozen section may be studied (Benedict), but this, too, may be difficult to diagnose, and it may be necessary to await paraffin sections.

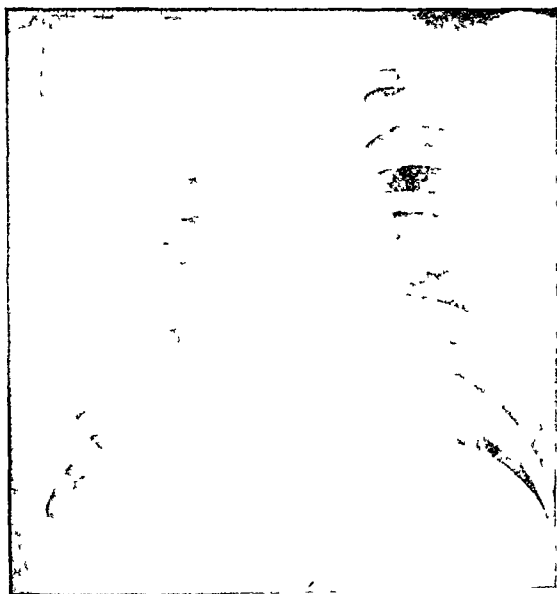


FIG. 459.—Bilateral extensive spherical pulmonary metastasis from a cylindromatous type of parotid tumor. There were no symptoms of lung involvement.

**Differential Diagnosis**—The *acute inflammations* of the parotid gland can be mistaken for tumor. However, usually the parotid gland is diffusely involved and tender, and there is frequently tenderness of the other parotid salivary gland. The submaxillary gland may also be involved by inflammatory processes, and it is not too infrequent to find either gland presenting secondary changes due to the presence of *stones* within their main ducts. With these calculi, there is increase in size and considerable induration of the entire gland. Frequently there are paroxysms of pain which coincide with meals. These painful crises are usually accompanied by very rapid swelling of the gland and tend to recur at shorter and shorter time intervals. Between meals the pain ceases. The calculus can often be felt by careful bimanual examination or it may be seen on roentgenographic examination. It may be impossible to canalize the excretory salivary canal and inject lipiodol because of the stenosis secondary to the inflammation. Inflammations, particularly of the submaxillary gland, can occur without formation of stones. Because of the adherence of the gland, diagnosis of tumor is often made.

It is often obvious that a primary tumor of the salivary glands exists, but it may be difficult to determine whether this tumor is a benign or a malignant mixed tumor. This determination is extremely important particularly when the tumor arises in the parotid gland, for the treatment of a benign tumor is much more conservative than that of a malignant. Table XXIII indicates some of the main differences. It is true that there are some cases in which it is impossible to differentiate and the decision must rely on a biopsy.

TABLE XXIII DIFFERENTIATION BETWEEN BENIGN AND MALIGNANT SALIVARY GLAND TUMORS

	BENIGN	MALIGNANT
Clinical history		
Rate of growth	Slow (years)	Rapid (months)
Sex	More frequent in females	No essential difference
Age	Peak before 40 years	Peak about 50 years
Pain	Usually absent	Invariably present
Physical examination		
Fixation	Freely movable	Often fixed to skin, deep structures, bone
Facial nerve paralysis (Parotid tumors)	Unusual	Common (about 33 per cent)
Consistency	Firm cystic nodular	May be stony hard
Gross pathology	Well circumscribed capsule, often shows cartilage	No capsule invasion of bone and contiguous tissue
Metastases	Never	Rather frequent (lymph nodes lungs bone)

**Roentgenologic Examination**—If the tumor is large and there is any suspicion of involvement of contiguous bony structures, the roentgenologic examination may reveal destructive processes in the base of the skull, the zygoma or the mandible. Sinulography may be useful as a roentgenologic procedure to demonstrate the presence or absence of distortion or involvement of the parotid salivary gland. Lipiodol is injected by a cannula inserted in Stensen's duct. Stereoscopic roentgenograms are taken immediately afterward. The findings have been well summarized by Kimm: "Tumors situated in the vicinity of the gland, *without actually involving it*, may cause a defect in the glandular shadow which is frequently associated with lack of or partial visualization of the smaller ducts in the affected region. Usually, the margin of the gland is well demarcated and this fact, together with a uniform radio density of the parenchyma ordinarily signifies a secondary effect due to pressure. On the other hand the *actual involvement of the gland* by tumor is manifested by abnormal markings of the ducts and by lack of a demarcation between the glandular parenchyma and the tumor. The ducts are irregular in their contour and distribution and may be visualized only partially if at all. Often, the parenchyma shows an irregularity in the radiodensity."

**Biopsy**—A biopsy of a malignant ulcerated lesion of the salivary gland may be done without difficulty. The nonulcerated salivary gland tumors present a problem however, for in the obviously malignant or benign lesions which are to be treated by surgery biopsy does not seem indicated. For the lesion in which the diagnosis and point of origin are debatable an aspiration biopsy may be diagnostic. The papillary cystadenoma lymphomatosum of the

almost entirely influenced by the presence of the facial nerve which is intimately associated with the gland. With an obvious but operable malignant tumor which has caused facial paralysis, a radical procedure is indicated and there should be no hesitation in permanently sacrificing the facial nerve. When regional lymph node enlargement due to a malignant tumor is present, then radical resection of the gland together with block dissection of the regional lymph nodes is warranted. An obviously benign tumor of the parotid gland brings up the question of whether to shell it out or remove it with its capsule. It seems reasonable that whenever it is possible the tumor, together with its capsule and a minimal amount of surrounding normal parotid tissue should be removed.

A not definitely malignant but operable tumor located in the region of the parotid gland should have a fairly radical resection without sacrificing the facial nerve if possible. In other instances the tumor may be intimately associated with the facial nerve so that complete surgical extirpation will be impossible without damage to it. If frozen section proves the tumor malignant, the decision should be to resect the facial nerve. If the tumor is one of the cylindromatous variety and the patient is rather young, then also a radical rather than conservative excision should probably be done. If the neoplasm is a typical benign mixed tumor, an attempt should be made to conserve the facial nerve. At times complete parotidectomy may have to be done, but if the technique of Bailey is used the nerve can be spared. The decision may be extremely difficult and many factors such as the age of the patient, the pathology of the lesion and the location of the tumor may have to be evaluated.

In cases in which a facial paralysis results from the operation, an adequate lid suture of the inner and outer canthus reduces the palpebral fissure and the possibilities of infection of the corner.

**RADIOTHERAPY.**—Although radiotherapy has been applied successfully to the treatment of salivary gland tumors, an appraisal of its true value has not been possible due to lack of correlation with the pathologic entities. A sizable series of cases treated by radiotherapy with histologic studies and sufficient follow up is yet to be produced.

The radiosensitivity of salivary gland tumors increases with their cellularity and consequently the benign mixed tumors react less favorably and less rapidly than the more cellular malignant tumors. In particular the cylindromatous variety of semimalignant tumors of the salivary gland show favorable response to irradiation. Radiotherapy should perhaps be employed as the primary treatment in tumors of the semimalignant variety when there is certainty that the surgical procedure will be a failure or surgical treatment is otherwise contraindicated.

On the basis of the radiosensitivity shown by some of these tumors, Ahlborn has employed and advocated postoperative radiotherapy. It is our opinion that if radiotherapy is to be used it has to be in sufficient amounts to attain total sterilization of the tumor and that this large dosage would not be justified when the tumor has been largely excised. If, however, the tumor has

Specific infections of the salivary glands are unusual. *Tuberculosis* may be present in a parotid node but is seldom primary within the gland. *Syphilis* is even rarer than tuberculosis. Only tertiary syphilis can simulate cancer, there is diffuse induration and sometimes enlargement of the lymph nodes with adherence to the skin. However, this process has a very slow evolution without facial paralysis, is nonpainful, and infrequently bilateral. Another specific evidence of syphilis is a positive serology. *Actinomycosis* is an extreme rarity which can be diagnosed either by examination of the secretion in the ulceration or by biopsy. There is no facial paralysis, the lymph nodes are not often enlarged and there may be some trismus. If fistulas exist they exude yellowish pus. In both the fistulas and the ulcerations typical sulfur granules may be observed on the smear.

*Milium cysts* are accompanied by a symmetrical bilateral swelling of the neck which often simultaneously involves the parotid submaxillary and sublingual salivary glands and, in addition, the pilosebaceous and lacrimal glands. This disease is a very slowly progressive process without facial paralysis.

In a few instances a primary ulcerated skin carcinoma particularly in the region of the parotid gland could be confused with a malignant salivary gland tumor. If the skin carcinoma is early, the diagnosis is not difficult but if it is advanced and the history is poor the clinical diagnosis may be obscure. Biopsy, however usually clarifies this question.

*Metastatic malignant lesions* in the lymphatic tissue around the parotid and submaxillary glands give the most difficulty in differential diagnosis, the greater majority of these metastases are found in the latter location. In the region of the parotid gland skin carcinomas and melanomas arising from the eye can metastasize to the preauricular lymph node or nodes directly within the substance of the parotid gland. Early, the metastasis is usually manifested as a well defined nodule. The skin carcinoma or the melanoma may have been treated years before and the scar may be inconspicuous, thus an erroneous diagnosis of a primary parotid salivary gland tumor may be made. In the region of the submaxillary gland metastases are usually derived from the skin, oral cavity or sinuses (Fig. 441). The tumor arising from the oral cavity may come from the lip, floor of the mouth, gingivae or buccal mucosa but a primary lesion may exceptionally be found in the nasal fossa, nasopharynx or oropharynx. It is also possible at times for metastatic lymphosarcoma to be taken for a primary lymphosarcoma of the salivary gland. Aspiration biopsy of the submaxillary nodule frequently reveals metastatic epidermoid carcinoma. In rare instances primary tumors far from the oral cavity may metastasize to the submaxillary lymph nodes.

### Treatment

**Surgery**—The best treatment for the majority of salivary gland tumors is a surgical excision. If the tumor whether it be benign or malignant arises within the submaxillary gland there are no important neighboring structures susceptible to injury and therefore radical removal of the tumor is indicated. For the tumors which arise in the region of the parotid gland treatment is

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## TUMORS OF THE PANCREAS

### Anatomy

The pancreas is a gland which extends from the second portion of the duodenum to the spleen, following an almost transversal direction at a height of the first two lumbar vertebrae (Fig. 160). It measures 15 cm in length, 4 to 5 cm in height and about 3 cm in thickness and has an irregular surface. The pancreas is usually divided into the head, the body, and the tail. The head of the pancreas is situated at the first three parts of the duodenum. The body and tail extend from the head. Its secretion is secreted into the duodenum.

The anterior surface of the pancreas is covered by the peritoneum and crossed by the superior mesenteric artery. The suprapancreatic area is in contact with loops of the duodenum.

covered by  
peritoneum  
crossed by  
superior  
mesenteric  
artery  
or

been incompletely removed or there is evidence of postoperative recurrence in a tumor of the semimalignant or malignant variety a thorough course of roentgentherapy is justified as the only additional recourse

### Prognosis

The prognosis of salivary gland tumors changes according to the pathology and the type of treatment given. In the benign mixed tumors particularly in the region of the submaxillary gland which have had a wide excision, the percentage of recurrences is negligible (Dockerty). If, however, surgery is limited, particularly in the region of the parotid gland where an effort is made to avoid facial nerve paralysis the incidence of recurrence is high. The percentage of recurrences increases the longer follow up is continued for these tumors have been known to recur twenty and even forty years after removal. The type of excision done is probably just as important as the microscopic appearance of the tumor. There is no doubt that if attempts are made to predict recurrence on the basis of histology alone many errors will be made. For instance, the experience of McFarland (1943) is often quoted. He submitted mixed tumors to twenty five competent pathologists and asked them to answer the question "Do you think this tumor will recur?" The answers were only 52 per cent correct. In 400 patients with mixed tumors on whom follow up was carried out by McFarland, 100 recurrences (25 per cent) appeared. Ninety six of these 400 patients were lost to follow up, and if they are eliminated the rate rises to 32 per cent. The recurrence rate for a group which was followed for five years was 40 per cent, and of those which were followed seven years the recurrence rate was over 60 per cent.

Surgical treatment of the malignant mixed tumors has a very poor survival rate. Stein and Geschlechter report five year survivals in three of twenty three patients. Hiltze had eight five year survivals in thirty one patients in whom excision had been done and who received postoperative radiation therapy. Ahlborn reported on thirty five patients treated by excision and radiation fourteen of whom were well and alive after five years.

Radiotherapy alone for benign mixed tumors may cause temporary disappearance or diminution in size of the tumor, but they generally recur. Irradiation alone for the malignant tumors gives variable results. Ahlborn reported nine of thirty nine patients treated with radiations alone who were without disease after five years. The results from radiotherapy also depend upon the pathology. The epidermoid carcinomas have the poorest prognosis, while the tumors which resemble the basal cell carcinomas or have a papillary cystic structure have the best. There are always a few patients in whom the response to radiotherapy is unexpected.

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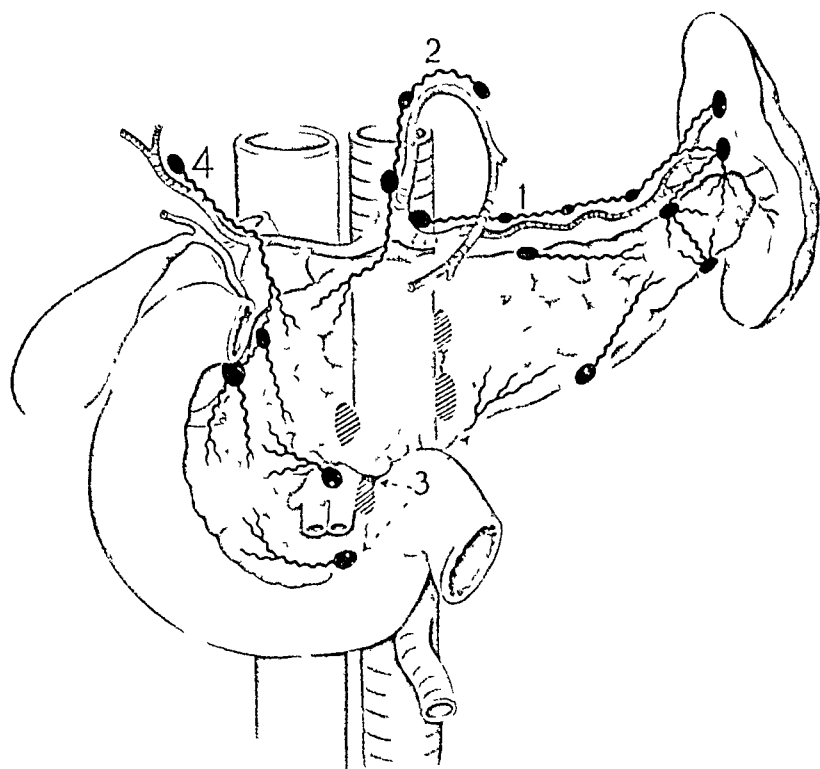


Fig 161—Schematic representation of the lymphatics of the pancreas drained by 1 trunks of the left side 2 superior trunks 3 inferior trunks and 4 trunks of the right side

the head is in direct relation with numerous vessels of the portal and caval systems. The posterior surface is covered by the ligament of Treitz. The body is anteriorly in direct relation with the stomach and posteriorly with the aorta and the left kidney and suprarenal gland. The tail has very variable relations but it is usually in direct contact with the spleen.

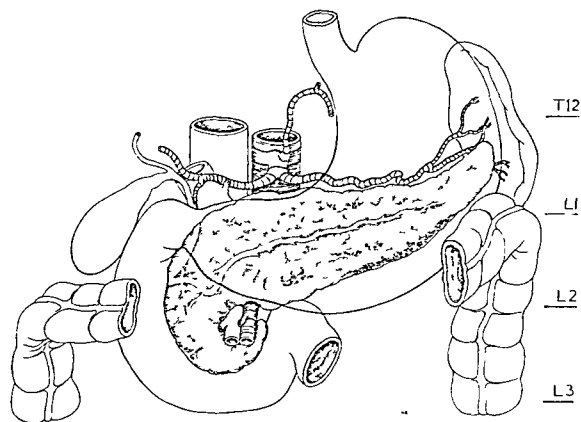


Fig. 460—Anatomic sketch of the pancreas showing the relationships to the three first portions of the duodenum, the common duct, the stomach, spleen and transverse colon. Note the projection of the organ in reference to the vertebrae.

The pancreas is a racemose gland similar to the salivary glands and is formed by secreting acini, each one of which constitutes a pancreas in miniature. The secretion of these acini is canalized toward the canal of Wirsung which extends from the tail toward the head of the gland. In addition in most instances there is an accessory canal the canal of Santorini which is 5 to 6 cm. long, is found in the upper half of the head of the pancreas and ends independently in the duodenum. The main pancreatic duct enters into the duodenum in conjunction with the common bile duct to form a common termination (ampulla) in about 55 per cent of the cases. In the rest there are various other anatomic arrangements. At the point where the main duct empties there is a smooth muscle sphincter.

The blood supply to the pancreas is derived from the superior pancreaticoduodenal, the inferior pancreaticoduodenal, and the splenic arteries. The principal veins accompany these arterial branches. In the celiac region there is a rich plexus of nerves which is formed by the sympathetics in the right vagus. These nerve trunks are related to the numerous ganglions which are

the bile ducts. Autopsy statistics, however, are more accurate today because complete dissection of the bile and pancreatic ducts is fairly frequently done. Carcinoma of the *head* makes up approximately two-thirds of all the malignant tumors of the pancreas. Carcinoma of the body probably makes up about one fourth of all the carcinomas of the pancreas. The number of cases of carcinoma of the *body* as compared with carcinoma of the head of the pancreas is somewhat determined by the stage of the disease because terminally carcinoma of the body may have extension to the head.

The *islet-cell tumors* of the pancreas make up a small but distinctive group of neoplasms. Their incidence is a matter of conjecture. Whipple (1942) found 134 reported in the literature. The incidence at autopsy varies somewhat according to the thoroughness of the examination and the ability to recognize the tumor.

### Pathology

**Gross Pathology**—In *carcinoma of the head* of the pancreas, the primary tumor is hard and the head is deformed by a nodular mass. On cut section the pancreas is replaced by homogeneous tumor obliterating the normal lobulated pancreatic tissue. The canal of Wirsung and the common bile duct are often obstructed and, at times, invaded by neoplastic masses. The obstruction of the common bile duct is often associated with carcinoma in the lymph nodes along the biliary tract. This neoplastic lymph node involvement results in invasion of the duct wall (Kaplan), which, in turn, fixes the duct and permits its compression instead of mere displacement. Because of the complete obstruction of the common bile duct, the gall bladder is usually distended, and the liver, too, is invariably enlarged, its color ranging from dark green to olive yellow. The longer the biliary obstruction is present, however, the smaller the size of the liver and the greater its connective tissue content. The bile ducts within the liver are always found dilated and there is increased interlobular and intralobular connective tissue. In the early stages of the biliary obstruction the bile is thick and inspissated, only later becoming pale and thin.

Cancer of the head of the pancreas tends to remain fairly well localized, for spread is blocked by the duodenum on three sides, by the proximal transverse colon, and by the posterior wall of the abdomen. Spread to the peritoneal cavity is restricted because the head is in contact with the peritoneum in only one small area near the lower margin of its anterior surface.

With spread of the tumor, the head of the pancreas becomes fixed by inflammation or neoplastic connective tissue. These adhesions firmly anchor the carcinoma to the stomach, the duodenum, the transverse colon, and the diaphragm, it also invariably becomes adherent to the retropancreatic tissue and vertebral column. The lesser omental cavity becomes smaller. These adhesions may even cause a partial pyloric obstruction. With further advance of the disease, the carcinoma infiltrates the musculature of the duodenum, stomach, or transverse colon, and this may result in mucosal edema and ulceration. It can even penetrate through the diaphragm to implant on the pleural

divided into two groups the superior, composed of the suprarenal splanchnic and juxtaceliac ganglions, and the inferior, formed by the aortic, mesenteric, and renal ganglions. The interior and inferior surfaces of the tail and body are covered only by peritoneum, the anterior surface facing the lesser peritoneal sac, and the inferior facing the general peritoneal cavity.

Pancreatic heterotopia is not at all unusual. Castro Barbosa collected from the literature 430 cases in which pancreatic tissue was found in 28 per cent of the cases in the wall of the duodenum (usually in the submucosa), 25 per cent in the stomach, and 16 per cent in the jejunum, rarer sites included the ileum, mesentery, omentum, spleen, and gall bladder.

**Lymphatics**—The lymphatics of the pancreas are very rich, having numerous communications with the lymphatics of the duodenum. They follow the interlobular spaces and come to the surface of the gland, where they follow the direction of the vessels and are drained by the following trunks (Bartels):

(1) The *trunks of the left side* empty into the nodes of the hilum of the spleen, the nodes of the pancreatic or splenic ligament, and those nodes found in the superior and inferior border of the tail of the pancreas.

(2) The *superior trunks* for the most part drain the body of the pancreas. They follow an upward direction and end in the superior pancreatic lymph nodes.

(3) The *inferior trunks* also drain the body of the pancreas and empty into the inferior pancreatic, the mesenteric, and the left lateroaortic lymph nodes.

(4) The *trunks of the right side* are divided into two groups: (a) the anterior lymphatics, which follow the anterior surface of the head, some toward the infrapyloric lymph nodes, the others downward toward pancreaticoduodenal and mesenteric lymph nodes; (b) the posterior lymphatics, which are emptied by the posterior pancreaticoduodenal lymph nodes and the lateroaortic lymph nodes on the right side (Fig. 461).

### Incidence and Etiology

Carcinoma of the pancreas is a relatively rare neoplasm, making up only 1 to 2 per cent of all forms of cancer. It predominates in males in a ratio of about 4 to 1 and occurs mainly between the ages of 30 and 70 years (peak age incidence in both sexes approximately 60). It is practically never found in patients less than 25 years old. There is no evidence that chronic pancreatitis, alcoholism, or syphilis have any etiologic significance in the production of carcinoma of the pancreas.

In 14,000 autopsies at Johns Hopkins University, there were fifty cases of primary carcinoma of the pancreas, of which twenty-eight occurred in the head, seven in the body, and ten in the tail, and in five most of the pancreas was diffusely involved (Duff). It is difficult to obtain an idea of the true incidence of carcinoma in the different parts of the gland, for carcinoma of the head of the pancreas is most frequent in clinical material, but carcinoma of the body and tail predominates in autopsy material (Duff). Undoubtedly also many cases diagnosed as carcinoma of the head of the pancreas arise within

Only a small percentage of the *islet-cell tumors* are carcinomas, and these metastasize first to regional lymph nodes and liver.

**Microscopic Pathology**—Carcinomas of the pancreas can be divided into three types—those arising from ducts, acini, and islet tissue. The carcinomas arising from the ducts are by far the most common. They are often accompanied by very prominent connective tissue reaction and the picture is easily confused by blockage of the main ducts. The cells of the acini are fragile and tend to be effaced by the process developing within the ducts. If the neoplastic process blocks the ducts for any length of time, the acinar cells disappear completely. On the other hand, the cells of the islands are very resistant and capable of proliferating and conserving their structural characteristics (Fig 462). There may be considerable dilatation of the ducts which can be cystic in nature and there may be papillary infoldings of the epithelium.

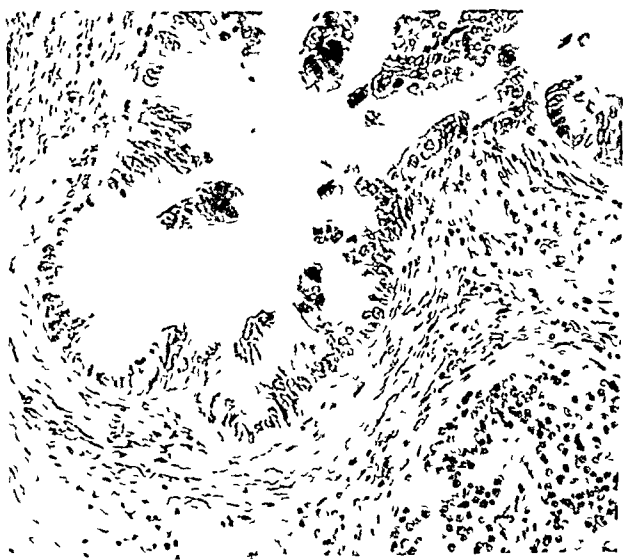


Fig 462—Photomicrograph of a well-differentiated adenocarcinoma of duct origin with fibrosis and persisting islet tissue (low-power enlargement)

At times there may be focal areas of squamous metaplasia which can also be mistaken for carcinomas arising from acini, but if enough sections are taken, their duct origin becomes apparent. The tumors which arise from acini are much fewer in number and resemble acini, and areas of transition between the tumor and the glandular acinar tissue can be observed.

The rare so-called *cystadenoma* arising from the ducts of the pancreas appears most frequently in the tail. In 1937, Young found only five in the records of the previous seventeen years at the Massachusetts General Hospital. These tumors show typically a multilocular cyst, the cavity of which is lined by papillomatous vegetations. They strikingly resemble the serous cystadeno-

and pericardial surfaces. The tumor often surrounds the portal vein, causing at times, thrombosis followed by ascites.

Carcinoma of the *body* and *tail* of the pancreas presents a large nodular mass which readily becomes fixed to the vertebral column and promptly involves the retropancreatic tissues. It may cause thrombosis of the splenic vein and infarction of the spleen. Posteriorly, spread may extend to the diaphragm, the left suprarenal gland, kidney, and spleen. The involvement of nerve trunks is also common in carcinoma of the body of the pancreas because these nerves (celiac plexus) are in intimate relation to the body. Involvement of nerves also occurs in the tail and head of the pancreas, but not as frequently.

Carcinomas of the body and tail are commonly associated with *venous thrombosis* (Sproul). In an extensive review of the literature and a careful study of a large group of cases, Sproul noted that 56 per cent of the patients with carcinoma of the body or the tail had at least one thrombus and 31 per cent had multiple venous thrombi. These figures are startlingly high. On the contrary if the carcinoma arose in the head, venous thrombi occurred in only about 10 per cent of the patients. Kenney found that carcinomas accompanied with multiple venous thrombi were of the mucinous type.

The *islet cell tumors* are usually situated in the body or the tail and may be within the substance of the gland or located on its surface. About one fourth of them appear at the head of the pancreas or at the junction of the body and tail. Islet cell tumors are well circumscribed and usually rather small, varying from a little over a millimeter up to 2 centimeters. They have a reddish gray color which contrasts sharply with the lobulated yellow of the pancreas. They may exhibit considerable fibrosis and calcification during their evolution because of regressive changes. When these tumors become malignant, which is rare they break through their capsule and invade the surrounding tissue. Multiple adenomas occur in about 10 per cent of the patients (Holman).

**METASTATIC SITE**—Metastases from carcinoma of the *head* of the pancreas most commonly involve the regional lymph nodes. The lymph nodes in the region of the head of the pancreas become fused by direct invasion of the tumor, and the hepatic duodenal chain of nodes becomes involved and may form large nodules of tumor in the neighborhood of the hilum of the liver. Later the mesenteric, preaortic, and posterior mediastinal lymph nodes can also be involved. Blood borne metastases to the liver as a rule are made up of rather small nodules which do not enlarge the organ. Other metastases to lungs and bones are not unusual. In a series of ninety nine autopsies on patients dying of carcinoma of the head of the pancreas, Leven found metastases to the lymph nodes in fifty and to the liver in fifty nine cases. Three presented supraclavicular lymph node metastases.

In contrast to the tendency of the carcinomas of the head of the pancreas to remain localized, those of the *body* and *tail* metastasize widely. Tumor spreads anteriorly to the peritoneal surface and then metastasizes to the nodes surrounding it thus forming a large tumor mass made up mainly of nodes. Widespread metastases particularly to the liver, lungs and bone are invariably present.

of the color of the urine and the clay color of the stools. There is obstruction of the biliary tree with dilatation of the extra- and intrahepatic ducts. With these changes there may be an apparent enlargement of the right lobe of the liver and the gall bladder may become palpable (50 to 65 per cent of the cases).

In a fairly high percentage of the cases, *pain* accompanies carcinoma of the pancreas, but it seldom precedes the appearance of jaundice. It is often continuous and tends to radiate to the right upper quadrant. At times the pain has a colicky nature, even in the absence of concomitant gallstones (about 20 per cent of the patients have associated gallstones).

Emaciation is a constant finding. In a few weeks the patient may lose twenty or thirty pounds. The muscles rapidly become atrophic and there are profound metabolic disturbances initiated by prolonged cholemia and extensive liver damage. This results in a natural tendency to hemorrhage, and, terminally, biliary infection is common.

*Carcinoma of the Body of the Pancreas (Pain Predominates)*—These tumors grow silently, tend to metastasize early because of their extensive close relation to the peritoneal cavity and because of this often present a mass in the epigastrium. This mass is made up mainly of metastatic nodes in the region of the primary carcinoma. With further development of the tumor, infringement on the abundant nerve plexus in the region of the body causes *pain* (Chauflard). Morgagni reported a case in which the intense pain was described by the patient as comparable to dogs tearing away the superior portion of the abdomen. In cancer of the body crises of pain occur without apparent reason, often taking place three or four hours after eating. It is relieved by sitting up and leaning forward or by lying on the right side with the legs drawn up and bending forward at the hips; it is increased by a recumbent position, probably because the solar plexus anterior to the vertebral column is placed under tension. Usually these pains are of short duration (fifteen minutes) but may occur more than once in a twenty-four hour period. They can be very regular or very irregular. The pain is usually more severe at night and makes sleep impossible. Ultimately these crises may either take on a paroxysmal character or be angiod in character, complicated by *vomiting*. In these instances the patient rests immobile, the arms inert and the face pale and shows marked anxiety and fear of imminent death. The pain often extends through to the back and radiates to the scapula, but its most permanent location is the epigastrium. Nerve involvement at times is accompanied by pigmentation of the skin, suggesting melanosis.

*Weight loss* is often rapid and occurs in nearly every case. Obstinate constipation is frequent. It is not too unusual to find an enlarged liver; in eleven of sixteen patients the liver was enlarged (Duff). The spleen may also be enlarged due to infarction. Jaundice is practically never present except terminally.

*Carcinoma of the Tail of the Pancreas*—Cancer of the tail of the pancreas has the most insidious development of all the pancreatic carcinomas. Usually emaciation, asthenia, vague indigestion, and anorexia prevail. The initial symptoms are frequently caused by metastases to the peritoneum, lungs, bones,

mas of the ovary, rarely they do become malignant (Lichtenstein), but it may be very difficult to determine microscopically whether they are benign or malignant. They are usually rather small but occasionally attain a fairly large size. These true tumors have to be distinguished from the pseudocysts which may occur following trauma or infection. With blockage of the ducts, retention cysts appear and occasionally they may result from defective development or be associated with polycystic disease of the kidney.

Histologically, *islet cell tumors* should resemble the islands of Langerhans. They should have a definite capsule and compress the adjacent pancreatic parenchyma (Warren). Their fibrous encapsulation is at times incomplete and they are usually quite well vascularized. Special fixatives and stains are necessary to bring out the histologic details (Bensley, Bayley, Gomori), the special stains showing that they are composed largely of abnormal beta cells. Infrequently islet cell tumors are malignant, but the criteria of malignancy are somewhat debatable. It has been shown that even invasion of the capsule or blood vessels does not necessarily indicate malignancy. Hinnen believes that only those cases which show invasion of neighboring organs or definite metastases are malignant. It is possible that years would have to elapse before metastases appear in some cases (Liantz, 1940). It is possible that heterotopic pancreatic tissue in the duodenum, stomach, jejunum, mesentery, spleen, gall bladder, etc. may give rise to carcinoma or hyperfunctioning insulin producing benign or malignant neoplastic tissue (Castro Barboza).

### Clinical Evolution

*Carcinoma of the Head of the Pancreas (Jaundice Predominates)*—The rich symptomatology of cancer of the pancreas is above all else a function of the extension of the tumor and symptoms are due to compression or invasion of neighboring organs. Therefore the clinical picture varies according to the site of origin of the tumor. The onset of cancer of the head is insidious. Often there is a preliminary period of weight loss, asthenia, slow digestion or vague indigestion, gaseous distention and nausea. In some rare instances the appearance of tenacious anorexia introduces the illness. These phenomena however are not too alarming. It is the appearance of jaundice or the sudden manifestation of a painful crisis to provoke a realization of actual illness.

The jaundice which accompanies a cancer of the pancreas has a very distinctive evolution. It may be preceded by an acute digestive episode associated with vomiting or diarrhea but more often it develops slowly and is consequently unobserved even by the patient. It appears first on the mucous membranes and the palms of the hands but gradually becomes generalized reaching a maximum intensity after a period of several weeks. The yellow color of the skin deepens little by little passing from a light yellow to a dark saffron and in certain instances to a greenish or olive color. Very rarely a veritable black jaundice occurs. Whatever its intensity the jaundice predominates generally on the face, the region of the genital organs and limbs. The jaundice is characterized by its persistence. It does not regress. With jaundice pruritus is usually severe. The patient often notes deepening



cinoma of the body and the tail, excruciating pain is often present. Occasionally pain is provoked by abdominal palpation. Careful questioning concerning the type of pain may give information which will suggest involvement of the celiac plexus (see Clinical Evolution). A high incidence of venous thrombi may suggest the diagnosis.

In summary, carcinoma of the body or tail of the pancreas should be suspected in males between 40 and 60 years with a palpable tumor mass in the epigastrium, extreme weight loss, pain, and peripheral venous thrombi.

The diagnosis of *islet-cell adenomas* is probably never made when symptoms of hypoglycemia are absent. If the symptoms of hypoglycemia and the clinical picture are substantiated by the typical laboratory findings, then the suspicion of islet-cell tumor can be nurtured.



FIG. 463—Widening of the loop of the duodenum with extensive mucosal destruction and irregularity of the third portion of the duodenum due to invasion by carcinoma of the pancreas.

**Roentgenologic Examination**—A large tumor of the head of the pancreas may displace the first and second portions of the duodenum to the right and the third portion downward. Widening of the duodenal curve alone is not diagnostic for it may be present in asthenic individuals or it may rarely be caused by an aneurysm of the pancreaticoduodenal or superior mesenteric artery or aorta. Irregularity and deformity of the pylorus and duodenum can occur from infiltrative encroachment (Fig. 463). Obstruction of the pylorus or of some part of the duodenum (usually the third portion) is a late finding.

and other organs. In carcinoma of the tail of the pancreas pain, although not nearly as common as in the body, radiates invariably to the left hypochondrium and left side of the chest. Jaundice almost never occurs. An abdominal tumor is one of the most common findings.

**Islet Cell Tumors of the Pancreas**—The symptoms which occur with islet cell tumors are those due to the overproduction of insulin. It is impossible to say what proportion of these tumors arising from islet tissue are functional—perhaps 70 per cent. However, practically all the patients in the lower age groups who have been reported on had symptoms of hypoglycemia. The size of the tumor bears no relation to the degree of hyperinsulinism. These symptoms are protean in nature, derive mainly from nervous system disturbances, and can be divided into three stages (Wuchope). With slight hypoglycemia there is fatigue, lassitude, indefinite restlessness, and malaise. These are followed by symptoms suggesting compensatory secretion of adrenalin: pallor, clammy perspiration, palpitation, tremor of the fingers, fear, sensation of hunger, lowered temperature, and increased pulse rate and blood pressure. The third stage resembles alcoholic intoxication with clouded sensorium, double vision, staggering, violence and hysteria. These advanced symptoms are easily confused with epilepsy or alcoholism. Blood sugar may be very low during an attack. Brain changes similar to those described in patients receiving overdosages of insulin have been reported (Malamud). If the tumor recurs after surgical removal of a carcinoma of islet cell origin, then hypoglycemic symptoms may appear with the recurrence. Benign islet cell tumors infrequently cause death. In malignant islet cell carcinomas death is caused by a combination of hypoglycemic reactions and wide dissemination of the neoplasm.

### Diagnosis

**Clinical Examination**—Carcinomas of the head of the pancreas are usually easily diagnosed by the progressive, obstinate, unrelenting jaundice which is usually accompanied by pain and profound weight loss. The laboratory findings all give evidence of complete biliary obstruction with acholia, a rising icterus index, and large amounts of bilirubin in the urine. The liver is frequently palpable and rather smooth; the gall bladder is enlarged in a high percentage of patients, no mass is felt in the region of the pancreas. When obstructive jaundice and pain, digestive disturbances and rapid weight loss occur in a male about 60 years of age carcinoma of the head of the pancreas should be strongly suspected.

Carcinomas of the body and tail of the pancreas are rarely diagnosed before surgical exploration or necropsy. In Ransom's series (1935) only three of sixteen cases were correctly diagnosed preoperatively. In Duff's group of nineteen cases none was diagnosed. Jaundice is practically never present in carcinoma of the body of the pancreas except terminally. In about one half of the patients a palpable tumor mass is present in the subumbilical region or in the region of the left hypochondrium. It is hard, quite sharply limited and gives an impression of resistance. If it is fixed to the vertebral column, it may be adherent to large vessels and may therefore pulsate. In both ear-

tests of external pancreatic function are somewhat complicated, they have been detailed recently by Bauman. Table XXIV summarizes some of the information which can be gained by laboratory examinations of the duodenal contents. In numerous instances, however, in spite of the most careful clinical and roentgenologic examination, differentiation may be resolved only by a prompt exploration. *Common duct lithiasis* may almost exactly mimic carcinoma of the head of the pancreas. Usually, however, the patients are younger and have a previous history of attacks of acute colicky pain; the biliary obstruction is not complete and weight loss and weakness are not as pronounced as in carcinoma of the pancreas. Further points of differentiation have been shown by Zollinger (Table XXV). Dilatation of the gall bladder is present in a high percentage of patients with carcinoma while it is practically never dilated in the presence of a biliary lithiasis even when the common bile duct is obstructed by a calculus. Courvoisier explains this by recalling that in cases of lithiasis obstruction is invariably preceded by an inflammatory process which scleroses the vicinity of the biliary tract and renders it less distensible.

TABLE XXIV DIFFERENTIAL DIAGNOSIS OF CARCINOMA OF PANCREAS AND OTHER CONDITIONS

	CARCINOMA OF HEAD OF PANCREAS	CARCINOMA OF AMPULLA	CARCINOMA OF COMMON BILE DUCT	OBSTRUCTION OF COMMON BILE DUCT DUE TO STONE
Bile in duodenal contents	Usually absent	Intermittently present	Usually absent	Intermittently present
Blood	Invariably ab- sent	Frequently pres- ent	Invariably ab- sent	Usually absent
Enzymatic fer- ments	Invariably ab- sent	Invariably ab- sent or greatly diminished	Invariably pres- ent	Invariably pres- ent
Gall bladder	Usually enlarged	Usually enlarged	Usually enlarged	Usually normal size
Röntgenologic examination	Occasional dis- placement of stomach and inversion of du- odenum widen- ing of its loop	May show filling defect	No useful find- ings	15 per cent of stones radio- opaque

TABLE XXV DIFFERENTIAL CHARACTERISTICS OF COMMON DUCT LITHIASIS AND CARCINOMA OF HEAD OF PANCREAS

(From Zollinger, R. and Kevorkian, A. N. New England J. Med., 1939)

SYMPTOM OF FINDING	COMMON DUCT STONE IN 75 CASES (%)	CARCINOMA OF THE HEAD OF THE PANCREAS IN 49 CASES (%)
Miles	13	69
1 em. dis.	87	31
Past history suggesting gall bladder disease	100	18
Colicky pain	91	16
Referred to dorsal region	67	18
Weight loss	25	86
Jaundice	81	86
Intermittent jaundice	35	12
Vomiting	77	37
Chills	33	8
Enlarged gall bladder	12	55
Enlarged liver	25	80

Positive obstruction can be demonstrated in about 37 per cent of the cases (Beik). If the tumor is of any considerable size and located in the body or tail of the pancreas, pressure deformity or invasion of the greater curvature of the stomach and duodenum may be observed.

If roentgenograms are taken in the prone lateral view a tumor of the pancreas may project anteriorly into the cavity of the stomach and thus be visible. Engel and Lysholm developed a roentgenologic technique in which effervescent powder with Vichy water is given. With the patient in a prone position lateral and anteroposterior roentgenograms are taken. The pancreatic tumor causes an increase of the retrogastric shadow which is thus made visible.

**Laboratory Examination**—The laboratory findings in carcinoma of the head of the pancreas all give evidence of complete biliary obstruction. The icterus index constantly increases and the van den Bergh test shows a direct reaction. Bile is prominent in the urine but absent in the stools. Urobilinogen is absent in the urine. At times there may be blood in the stool from ulceration of some part of the gastrointestinal tract. There may be increased tendency to intestinal hemorrhage because of liver damage. The tests of external pancreatic function are extremely important and should include a determination of pancreatic ferment activity (amylase, protease and lipase) and a quantitative estimation of fat absorption (Bauman). Johnson reported on thirty patients, sixteen of whom showed elevation of the serum lipase. Diminution of gastric acidity appears in a fair percentage of the patients. Glycosuria infrequently occurs in carcinoma of the pancreas but when present is found when the tumor involves the tail where the largest numbers of islets are found.

In *islet cell tumors* the evidence of origin can be substantiated by a positive assay for insulin in either the primary tumor or its metastasis. In the twenty one cases reported from the literature by Hanno in only three instances was it successful. Wilder (1927) made the first report. The fasting blood sugar must be 50 mg per 100 cc or less during an attack and the symptoms should be promptly alleviated by the administration of glucose by vein or mouth. The blood sugar after a fast of twelve to fifteen hours, is more reliable than the glucose tolerance curve which is more a liver function than a pancreatic function test (Whipple, 1942). Disorders of the suprarenal glands, anterior lobe of pituitary, liver, thyroid and thalamus in which hypoglycemia may also occur must be ruled out.

**Differential Diagnosis**—The differential diagnosis of carcinoma of the pancreas often concerns *common duct obstruction due to stone, chronic pancreatitis* or other carcinomas of the perampullary region.

The assessment of certain laboratory findings may be of very great differential value. It is of particular importance to determine whether the obstruction is complete. This can be determined by repeated examinations of the stools for the presence of bile and repeated examinations of the urine for the presence of urobilin. If urobilin and bile are constantly absent then the obstruction must be complete. The duodenal contents should be aspirated and assayed for the presence of bile pigment and pancreatic ferments. The

Dilatation of the gall bladder is not present in about 15 per cent of the patient with carcinoma of the head of the pancreas because of concomitant gallstones. Conversely, in relatively rare instances the gall bladder may be dilated when cystic duct obstruction from stone also compresses the common duct (Bruns *loc. cit.* 1942).

*Chronic pancreatitis* is a disease entity in which the clinical symptoms and laboratory examination may strongly suggest a carcinoma of the head of the pancreas. This similarity may not be resolved even at the time of surgical exploration, for the firmness of the pancreas due to inflammation may be easily mistaken for a carcinoma. If the region is biopsied and frozen section done, the may be chronic inflammation. Conversely, a negative biopsy of the pancreas does not by any rule out the presence of carcinoma. There have



FIG. 10. Chronic inflammation of the stomach and first portion of the duodenum due to a tumor next to the body of the pancreas.

been numerous cases reported in which short circuiting operations performed for a supposed carcinoma of the head of the pancreas have resulted in complete and permanent disappearance of symptoms. Usually, intrinsic liver disease, particularly *infectious hepatitis*, which occurs in younger individuals, is not a difficult differential diagnosis. Biliary obstruction is intermittent and the patients tend to improve spontaneously. Other *carcinomas of the periampullary region* can produce almost all the findings that are present in carcinoma of the head. Their differentiation has been detailed in the chapter on carcinoma of the gall bladder and extrahepatic ducts. However, exact differentiation is only of academic interest, for surgical treatment is the same in both.

The extreme pain which is present in carcinoma of the body is often confused with other painful lesions such as *intercostal neuralgia*, *diaphragmatic*



Fig 464—Displacement of the wall of the stomach by an enormous benign cyst of the pancreas. The defect in the wall of the stomach has smooth margins. There is also displacement of the duodenum and the colon.

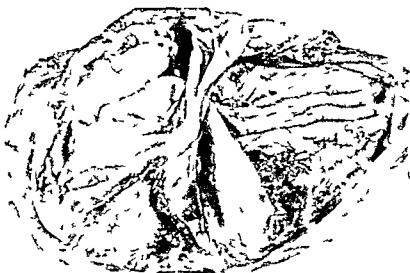


Fig 465—Gross specimen of large pancreatic cyst illustrated in Fig 464.

bolie changes have become irreversible, making operative risk prohibitive. It is to be hoped, in view of the somewhat encouraging results of surgery, that a more concerted effort will be made to bring patients with questionable carcinoma of the head of the pancreas to the experienced surgeon. It should be stressed that the patient with a questionable carcinoma of the head of the pancreas should not be observed over a long period of time while the diagnosis is being modified but rather should be explored promptly while the lesion may still be resectable. Brunschwig in 1937 reported one of the first successful operations in which the duodenum and entire head of the pancreas were removed for carcinoma. Numerous modifications have been introduced by practically every surgeon concerned with the operation. The techniques for resection of carcinomas of the head of the pancreas and of other tumors of the perampullary region are the same, as well as the establishment of intestinal

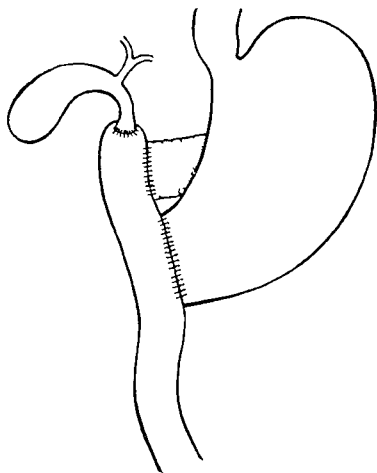


Fig. 467—A sketch illustrating the Whipple technique of pancreatoduodenectomy. The common duct and the remaining portion of the pancreas are anastomosed to the small bowel. These anastomoses are proximal to the gastroduodenostomy, thereby reducing the chances of ascending biliary tract infection.

continuity. At the present time the one-stage operation of Whipple seems to be most popular and logical (Fig. 467). This eliminates the dangers of two anesthetics and two major procedures. Extensive adhesions tend to form after the first stage and make the second stage more difficult. Whipple (1945) has performed nineteen one-stage operations with a postoperative mortality of only 31 per cent and he has lost no patients with the one-stage procedure for benign lesions.

In this operation certain principles should be adhered to. After resection of the tumor, the remaining free segment of the jejunum should be sutured to the common bile duct rather than to the gall bladder. This is done to reduce the incidence of biliary fistulas and also because the bile drainage is invariably better. The pancreas is also anastomosed to the jejunum. Person demonstrated that pancreatic secretions do gain entrance to the gastrointestinal

*pleurisy*, and *renal calculus* (Levy, Lichtman) It may even suggest a tabetic crisis If, however, profound weight loss with peripheral venous thrombosis is present together with a palpable epigastric mass, this should strongly suggest carcinoma of the pancreas We have seen a case in which secondary implantation had occurred on the serosal surface of the large bowel and signs suggesting a primary large bowel tumor were present

Metastases to the pancreas from primary lesions elsewhere are relatively infrequent, they occur in about 5 per cent of carcinomas of the lung, widely disseminating tumors such as the malignant melanoma, and choriocarcinoma

*Neoplastic cysts* of the pancreas are extremely rare They usually appear in middle life, are most frequent in the region of the body and tail, and may grow to a very large size (Kennard) Diabetes is present in about three of five patients with such cysts (Bowers) and there is quite frequently a history of disease of the biliary tract Examination usually shows a rounded mass in the upper portion of the abdomen Roentgenograms may reveal displacement of the colon downward with displacement of the stomach medially (Bowers) (Figs 464 465 and 466) Intravenous pyelograms may at times reveal poor function of the left kidney because of pressure of the cyst on the renal veins or artery

In *cystadenomas* of the pancreas arising in the body or the tail, the stomach is often displaced from its normal position by the cyst and there is usually a soft tissue mass in the left upper quadrant of the abdomen These tumors should be extirpated Diabetes, if present may improve after operation

### Treatment

**ROENTGENTHERAPY**—The value of roentgentherapy for advanced carcinoma of the pancreas was first demonstrated by Richards (1922) It should be emphasized however, that chronic pancreatitis often exactly mimics carcinoma and that unless there is pathologic proof no claims can be made as to cures

**SURGERY**—Surgical resection for carcinoma of the head of the pancreas as an operative procedure has been perfected during the past decade largely through the efforts of such men as Whipple, Lunschwig, Orr and others This formidable procedure requires meticulous pre and postoperative care and a surgeon of outstanding ability Unfortunately, these patients are extremely poor operative risks They may have fatty metamorphosis of the liver, reduced prothrombin time with increased tendency to hemorrhage, reduced serum proteins and often considerable weight loss In the preparation for surgery anemia when present should be corrected by transfusions fat in the liver should be displaced by high protein and high carbohydrate diet and prothrombin levels should be brought to normal by vitamin K Tube feedings may be necessary to combat anorexia and weight loss, the chlorides may have to be brought to normal and repeated lavage of the stomach will reduce its dilatation Spinal anesthesia has greatly contributed in making the long procedure possible with a minimum of complications

It is unfortunate that the number of patients suitable for this radical operation remains small Practically all patients when first seen are inoperable because of extension of carcinoma or because liver damage and other meta



be low In twenty-seven patients surgically treated by him the operative mortality was only 11 per cent

The benign *islet-cell adenomas* do very well following excision The malignant tumors of islet-cell origin have a rapid clinical course, usually with a hopeless prognosis However, Whipple (1945) reports one patient with a five-year survival of carcinoma of islet-cell origin following a one-stage procedure

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tinal tract following this procedure. Both of these anastomoses are proximal to the anastomosis of the stomach to the jejunum. This is done so that the passage of gastric contents will be distal to the anastomoses and thus ascending infection of pancreas and liver is substantially reduced. The postoperative care is directed to maintaining normal blood serum protein and prothrombin levels. Prophylactic penicillin should be used.

Almost none of the patients with carcinoma of the *body* of the pancreas are operable because when diagnosed they invariably have extensive metastases. The mass is made up mainly of metastatic lymph nodes. Brunschwig (1944) reported on six patients in whom he resected the body of the pancreas with splenectomy. There are only isolated reports of cures of carcinoma of the body and tail of the pancreas.

In *islet cell tumors* exploration is indicated. If an adenoma is found, it should be resected. Very careful exploration may not reveal an adenoma and the surgeon convinced of the clinical syndrome may do a subtotal removal of the pancreas. At the subsequent careful pathologic examination of the specimen, tumor may be found, hyperplasia of the islet cells may exist, or the pancreas may be normal. In fourteen patients in whom subtotal resection of the pancreas for hyperplasia of islet cells was done and subsequent histologic examination showed normal pancreas ten patients were cured (David). It should be remembered that symptoms may continue after removal of an adenoma because adenomas tend to be multiple and reexploration may be necessary. At times symptoms may be due to adenomatosis of islet cells (Frantz 1944). It is remotely possible that hypoglycemic symptoms may be caused by pathologic alterations in an aberrant pancreas. Whipple (1945) emphasized that patients with characteristic symptoms of an adenoma should not be denied operation because there is a chance first that such a benign tumor may develop into a malignant one and second that repeated attacks of prolonged hypoglycemia may lead to mental deterioration. In the malignant islet cell tumors radical resection of the pancreas is indicated if technically possible.

### Prognosis

In untreated cases of carcinoma of the pancreas about 90 per cent of the patients die within a year of the time the diagnosis is made, while in many the total duration of illness is less than six months. Even in the very small percentage of cases which are surgically resected the prognosis is usually unfavorable. In the eight cases of carcinoma of the head of the pancreas reported by Brunschwig all patients but one were dead at the time of the report, and follow up on this one was continued for only three months. Carcinomas of the *body* and the *tail* have an even more unfavorable outlook, Gordon Taylor (1934) reported on a patient who survived seven years.

Palliative surgical procedures to relieve jaundice vary. Cholecystostomy involves a high operative mortality—52 per cent in a series of Fraser. In the same series 66 per cent of the patients died within six months and 90 per cent within twelve months. Sallick indicates that while biliary intestinal anastomoses carry a high operative mortality external biliary drainage may

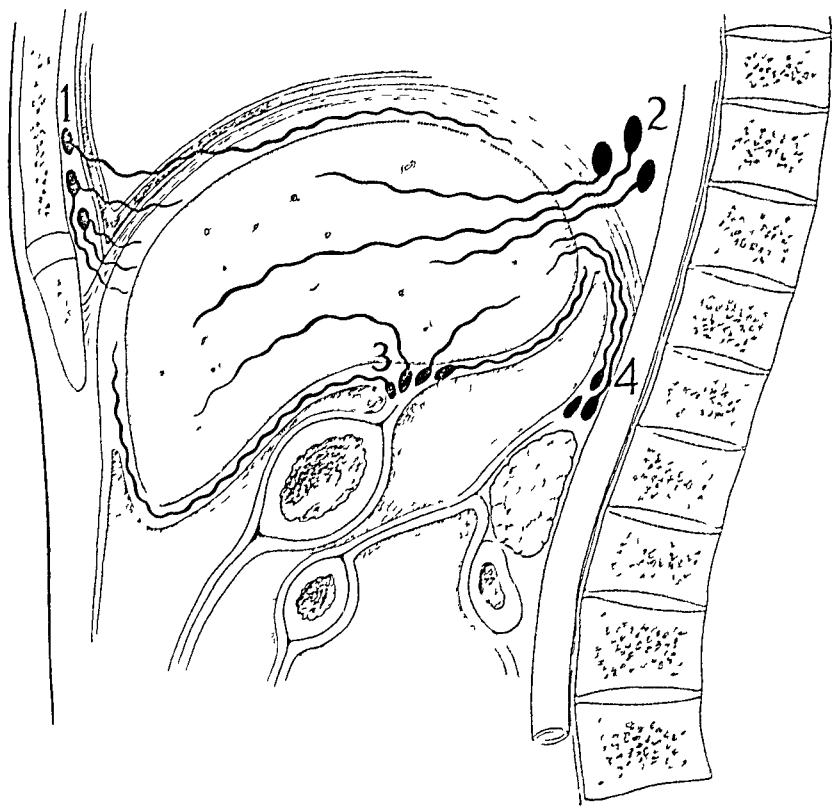


FIG. 108. Anatomical sketch of the superficial and deep lymphatics of the liver leading to 1, the periportal nodes; 2, the juxtaphrenic nodes of the posterior mediastinum; 3, nodes of the hepatic portal inferior vena cava and hepatic artery; and 4, nodes of the coronary chain and renal artery.

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## TUMORS OF THE LIVER

### Anatomy

The liver occupies a subdiaphragmatic position from the fifth rib and midclavicular line on the left side to the inferior costal margin and mid axillary line on the right. Formed as a caudate portion of the septum transversum, it retains this position attached by the bare area of its right lobe to the diaphragm posterosuperiorly. Being an extraperitoneal organ the parietal peritoneum is reflected in this area as the coronary and triangular ligaments. Anteriorly and inferiorly the liver retains its ventromesogastrium which carries the ligamentum teres to the anterior surface and the hepatic ducts and vessels to the porta hepatis of the inferior surface. The organ is divided into a right and left lobe by the peritoneal reflections to the contained embryonic vascular remnants of the umbilical vein and portal venous shunt. The quadrate and caudate lobes are divisions of the right main lobe.

The right suprarenal gland inferior vena cava vessel and gall bladder are all in direct contact with the hepatic capsule. The right kidney and colic flexure proximal duodenum and anterior gastric wall bear close relations to the



FIG. 118—Anatomic sketch of the superficial and deep lymphatics of the liver leading to 1 the pericardial nodes 2 the juxtaphepatic nodes of the posterior mediastinum 3 nodes of the hepatic portal inferior vena cava and hepatic artery and 4 nodes of the coronary chain and renal arteries.

inferior surface in the peritoneal cavity. The hepatic branch of the celiac plexus and portal veins furnish the entire blood supply. Biliary secretion is transmitted from the left and caudate lobe to the left hepatic duct and from the right and quadrate lobe to the right hepatic duct.

**Lymphatics**—The lymphatics of the liver are divided into two categories, the superficial and the deep. The superficial lymphatics arise from the superficial lobules and go directly to the surface where they travel beneath the peritoneum. Some of the superficial lymphatics of the liver enter the suspensory or the coronary or the triangular ligaments, pass through the diaphragm and end in the pericardial and juxtaphrenic nodes of the posterior mediastinum. Others follow the direction of the esophagus descending to end in the nodes of the coronary chain and still others travel toward the lower aspect of the liver and end in the nodes of the hepatic pedicle and inferior vena cava (Fig. 468).

The deep lymphatics arise from deep lobules and follow the trajectory of the portal and suprahepatic veins. They may also pass through the diaphragm with the vena cava and end in the supradiaphragmatic nodes. Others, however, follow the course of the branches of the portal vein receiving in their course the lymphatics of the biliary tree, and end in the nodes of the hepatic pedicle and the hepatic artery or coronary chain. A few may end in the juxtaportic nodes neighboring the renal arteries (Rouviere).

### Incidence and Etiology

Primary carcinoma of the liver is rare in the United States. The incidence based on mortality statistics is not valid because the diagnosis of cancer of the liver is too indiscriminately used in death certificates, usually in place of metastatic carcinoma or simply for undiagnosed intra-abdominal tumors. The peak age incidence is between the fifth and sixth decades. That it can occasionally occur in children was shown by Steiner (1938) who collected 77 cases in patients under 16 years of age, of these cases 53 per cent were in infants under 2 years of age. This form of tumor occurs in males more often than in females in a ratio of 7 to 3.

Primary carcinoma of the liver is found rather frequently in Japanese, Chinese, and Malaysians as well as in some natives of South Africa. In a series of 447 malignant tumors found in Java by Snijders 83 (18 per cent) were primary carcinomas of the liver. Berman reported that 83 per cent of his cases found in the Bantu races of South Africa were in males 40 years of age or younger. Kennaugh studied the incidence of carcinoma of the liver in the American Negro but did not find any increased incidence in relation to the white population. On the basis of this one could conclude that the natives of Africa are subject to some extrinsic factor such as diet which causes a high incidence of carcinoma of the liver (Gilbert). Fig. 469 illustrates the striking difference in the frequency of primary carcinoma of the liver in various races. The cause of these differences is as yet unknown but the incidence of carcinoma parallels the incidence of cirrhosis.

Cirrhosis is commonly associated with carcinoma of the liver. It seems to precede the development of carcinoma of the liver-cell type. The prevalence

of cirrhosis governs the incidence of primary carcinoma of the liver. In Europe and in the United States the incidence of cirrhosis of the liver is low, encountered in only about 2 per cent of the autopsies. The incidence of cirrhosis at autopsy has been reported as 5.8 per cent in Chinese men, and as 6.9 per cent in Malay men (Bonne). The incidence is still greater (10 per cent) in autopsies performed on the natives of the East Coast of South Africa (Fischer, 1929). In a series of almost two thousand cases of cirrhosis of the liver collected from the literature by Berk, 4.5 per cent had coincidental carcinoma. Stewart reported 124 cases of cirrhosis in which there was an incidence of 7 per cent of primary carcinoma of the liver. The association of cirrhosis with hemochromatosis does not change the incidence of carcinoma. Sheldon felt that the cirrhosis rather than the pigmentation was responsible for the neoplastic changes. In children with primary carcinoma of the liver there is practically never any pre-existing cirrhosis (Steiner), and its occurrence is therefore probably related to some congenital factor. It is also true that the liver-cell carcinoma in children may be associated with embryonic rests (Yamagiwa).

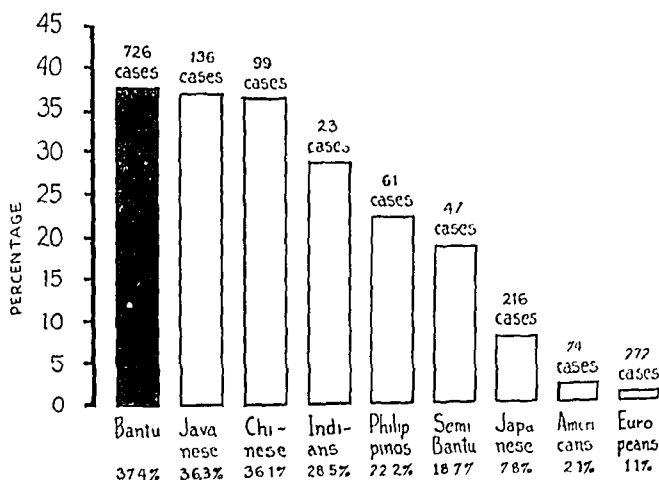


Fig. 169.—Comparison of the variable incidences expressed in percentage of all forms of cancer and of primary carcinoma of the liver in different races (From Berlin, C. South Africa J. M. Sc. 1910).

Intestinal parasitism, schistosomiasis, or distomiasis have been found associated with primary carcinoma of the liver and have been incriminated as causative agents. It has also been suggested that they may be connected with the production of liver cirrhosis. It is, however, likely that their presence is coincidental rather than causal.

Carcinoma of the bile-duct-cell type is only infrequently associated with cirrhosis and rarely arises on the basis of a congenital cyst (Willis). However, in the presence of a long-standing disease of the intrahepatic ducts, with resulting chronic inflammation, fibrosis, cyst formation, cholelithiasis, and infection of the bile, such changes may lead to the development of carcinoma (Yamagiwa, Sanes).

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and from there to the heart where they pass to the systemic circulation and eventually to the hepatic artery and to the liver. Other tumors, such as cancer of the breast may reach the liver through the lymphatics, and still others, such as carcinoma of the stomach may invade the liver directly. The liver also seems to be a very fertile soil for the growth of tumors of all types, which probably enhances the frequent finding of metastatic tumor there.

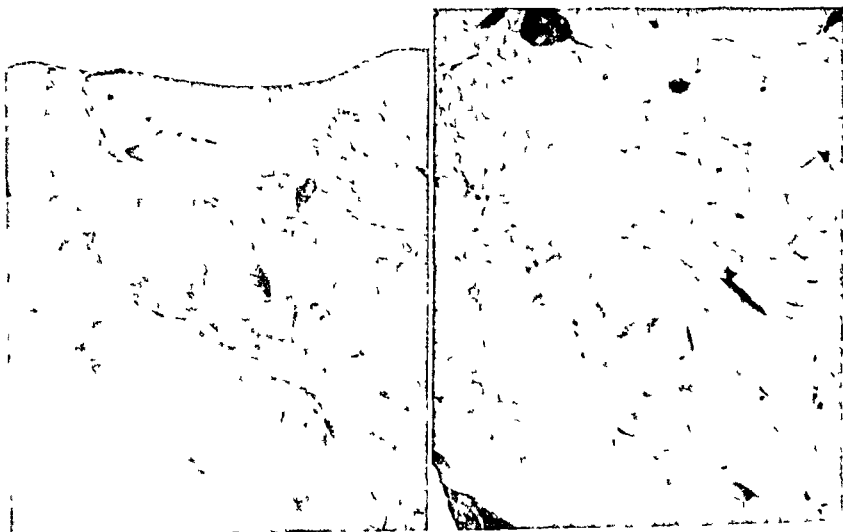


Fig. 171

Fig. 172

FIG. 171—Gross specimen of a primary carcinoma of the liver developing diffusely in the absence of cirrhosis. (Specimen contributed by Dr. Robert A. Moore, Department of Pathology, Washington University School of Medicine, St. Louis, Mo.)

FIG. 172—Gross specimen of a primary carcinoma developing in a cirrhotic liver. Notice the small nodules, thin bands of fibrous tissue, and pronounced vein invasion by tumor. (Specimen contributed by Dr. Robert A. Moore, Department of Pathology, Washington University School of Medicine, St. Louis, Mo.)

In metastatic carcinoma, the liver itself is tremendously enlarged. This is particularly true of a metastatic melanocarcinoma which may weigh as much as 10 kilograms. It should be remembered, however, that the liver can be extensively seeded with metastases and yet weigh within normal limits. The metastatic nodules of the liver are usually spherical and are often seen bulging beneath a tense elevated capsule. These metastatic nodules will vary somewhat in appearance according to their vascularity and connective tissue content. Their size will vary from a few millimeters to that of an entire lobe. As they increase in size, secondary changes with hemorrhage and central necrosis occur which give the nodulation a typical umbilicated appearance (Fig. 175). With the growth of the tumor, compression and destruction of the contiguous liver parenchyma occur. Not infrequently tumor will be found in the branches of the portal vein. Metastatic carcinoma of the liver is found more frequently than metastatic sarcomas. Sarcomas as a group are more cellular and softer and therefore more readily subjected to degenerative changes.

# Pathology

**Gross Pathology**—Tumors arising from the liver may form a large, single nodule (Fig 470) but very frequently have satellite tumor nodules around them (Fig 471). Another form presents a diffuse nodulation throughout the organ, usually with evidence of coexisting cirrhosis (Fig 472). This cirrhosis is of the Laennec type and because of it there may be evidence of collateral circulation, portal obstruction with ascites, esophageal varices, and splenic enlargement. The liver itself is, for the most part, enlarged. In forty-two cases reported by Berman, of which forty-one were of the liver cell type, the average weight of the liver was around 4,000 grams. Gross evidence of blood vessel invasion is frequently seen and it is not unusual to find evidence of invasion of the vena cava. Tumor thrombosis of the inferior vena cava and of the right auricle may occur (Gregory). Direct invasion of the diaphragm, gall bladder, and pleura sometimes occurs, and sometimes there is involvement of the mesentery and peritoneum.

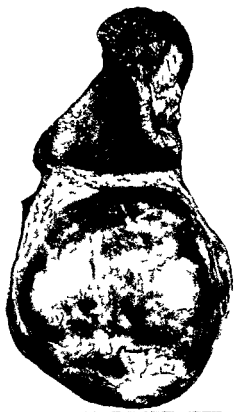


Fig 470—Surgical specimen of a well encapsulated pedunculated hepatoma of the liver

The liver is very often the site of metastatic disease. This is due for the most part to the abundant vascular supply to the liver from the widely ramifying portal system and from the hepatic artery. The portal system drains the pancreas, the large bowel, and the stomach and also has numerous anastomoses with the caval system. Tumors which develop in the lung, whether primary or metastatic, easily break into the branches of the pulmonary veins.

tumor between them may be difficult to differentiate histologically. Warvi's (1944) classification allows for these variations

- I Hepatomas
  - A Liver cell adenomas
  - B Liver cell carcinomas (with or without cirrhosis)
- II Cholangiomas
  - A Adenomas of intrahepatic bile ducts (solid or cystic)
  - B Duct cell carcinomas
- III Cholangiohepatomas (with both liver cell and duct cell elements)
- IV Primary tumors of the liver without specific hepatic elements (vascular, fibrous, epithelial rests, etc.)



Fig. 471.—Photomicrograph of the bile duct type adenocarcinoma of the liver. Note dilated bile duct with carcinoma originating from it. (From Sanes S. Am J Path. 1942.)

The consensus of opinion is that primary carcinomas of the liver are unicentric rather than multicentric and that the reason for the apparent multiplicity of lesions is readily explained because of the early distribution of tumor through the blood vessels.

### Clinical Evolution

About two thirds of all carcinomas of the liver have a clinical onset characterized by indefinite abdominal symptoms usually attributed to gastric disturbances (Berman). Nausea and vomiting may be present with a sense of

**METASTATIC SITE**—Because of the tendency of carcinoma of the liver to invade the hepatic and portal veins, particularly the latter, local spread within the liver occurs early and tumor easily migrates to the heart and thence to the lungs. In 89 per cent of the cases of primary carcinoma of the liver reported by Permin, the lungs were involved with metastatic disease. The second most common sites of metastases were the hilar, portal, mesenteric and retroperitoneal nodes. Metastases have also been found in the heart (Culpepper), brain, and skeletal system (Berman).

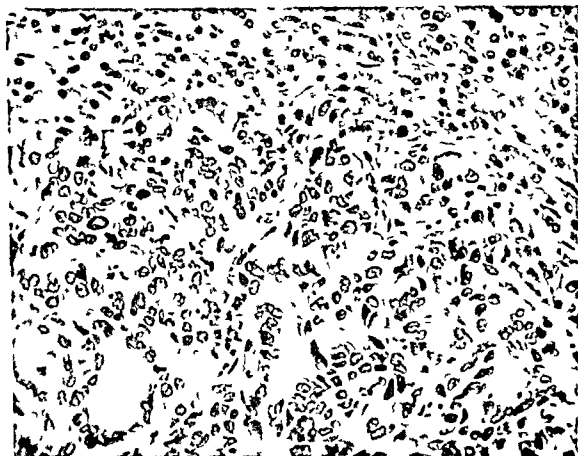


Fig. 471. Photomicrograph of a primary carcinoma of the liver-cell type. Note extensive invasion and bizarre forms of cells (H. E. stain, × 400).

**Microscopic Pathology**—Primary carcinomas of the liver are perhaps better classified as carcinomas of the liver cell type (hepatoma) and carcinomas of the bile duct cell type (cholangioma). There is frequently great variation in the microscopic pathology of the tumors of the liver cell type (Fig. 471) while the bile duct cell type has a very uniform pattern (Loesch). Yamagawa emphasized that there is usually a well developed capillary stroma in the liver cell type which is absent in the bile duct cell variety. The liver cell variety frequently produces bile which may be present in the metastases as well as in the primary tumor (Steiner). Bile secretion is not usually found in the bile duct carcinomas but at times bile pigment is present within the lumina of the small bile ducts (Wintermeyer). There may be benign and malignant tumors of both the liver cell and bile duct cell types and transitional forms of

hippuric acid test only shows changes when extensive liver replacement has taken place and after the clinical diagnosis is obvious.

The icterus index is usually only slightly elevated in carcinoma of the liver if there is no biliary obstruction due to metastatic nodes. The van den Bergh test may show an immediate direct reaction, however. The cephalin cholesterol test may be negative in carcinoma of the liver without cirrhosis, and, if this is found, will be of value in the differential diagnosis. The prothrombin time, in spite of extensive replacement, can be normal.

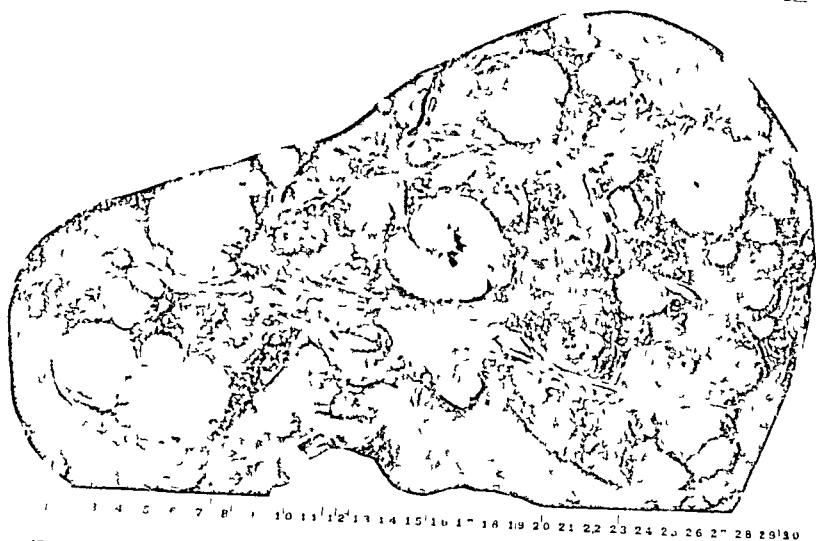


Fig. 475—Gross specimen of metastatic carcinoma of the liver with typical nodular replacement. Note variation in size and areas of central necrosis.

**Biopsy**—We have found that an aspiration biopsy, particularly when nodules are situated close to the anterior abdominal wall and are easily felt, may be of definite value. Certainly, a pathologic diagnosis on aspirated material would obviate a major surgical procedure, and, when positive, would quickly solve the problem of diagnosis and subsequent treatment. Recently, Gillman, using a new type of needle and improved technique, performed 500 aspiration biopsies with only one fatality due to a puncture of a large artery. Failure to obtain adequate tissue occurred in only 5 per cent. If the liver is involved by a diffuse process, an aspiration will undoubtedly bring positive results, but if the pathologic process is localized, then only a positive finding is significant (Gillman).

**Differential Diagnosis**—A metastatic carcinoma of the liver is considerably more frequently found than a primary tumor and, for this reason, the first effort should always be to eliminate this probability. The liver is often the site of metastases from primary tumors of the stomach, bowel endo

fullness and abdominal pressure in the epigastrium. Constipation occurs rather frequently. Pain is generally present in the form of a dull ache frequently localized to the right hypochondrium. It becomes more severe as the disease progresses but bears no relation to digestion. The increase of pain is explained by the progressive distention of the liver capsule or invasion of the diaphragm. When jaundice is present, it is usually minimal. Anemia and asthenia are remarkably constant and alarmingly progressive. Weight loss is observed in most cases but may be obscured by the presence of ascites or edema. Dyspnea occurs as a late symptom and is usually related to ascites, anemia, and pulmonary metastases. Hematemesis due to esophageal varices or invasion of the stomach may also be observed in advanced cases.

The liver is invariably enlarged, particularly the right lobe, and occasionally the total growth may be outlined from week to week. There may be a dilatation of the superficial veins of the chest and abdomen preceded by edema of the lower extremities. The dilatation probably occurs because hepatic invasion by tumor interferes with the portal circulation as an important collateral return (Gregory).

About one third of all carcinomas of the liver present an exceptional clinical onset, but they may be found only at autopsy. Berman described an acute abdominal type characterized by intraperitoneal hemorrhage. In some of his patients there was a febrile onset which often suggested a liver abscess. A small number of occult carcinomas were diagnosed at autopsy.

### Diagnosis

Because carcinoma of the liver is comparatively rare in this hemisphere the clinician is often reluctant to diagnose it and the disease may develop for several months before a diagnosis is established. Examination invariably reveals an enlarged tender liver, and if there is coexisting cirrhosis, there may be ascites, edema, evidence of circulatory changes, and hematemesis. The ascitic fluid is quite frequently blood tinged, and it is not too infrequent for carcinomas of the liver to produce fatal hemorrhage. Rarely, in the presence of evident thrombosis of the inferior vena cava, there is a sudden increase of edema of the extremities and in the size and tenderness of the liver accompanied by orthopnea and increasing venous pressure. These changes should be interpreted as evidence of a tumor thrombosis of the right auricle (Gregory).

**Röntgenologic Examination**—A roentgenogram is of value in establishing evidence of deformity of the liver and invasion of the diaphragm. The radioscopic examination furnishes information as to the fixation of the right side of the diaphragm. In certain instances due to tumor emboli there may be extremely prominent vascular markings seen by roentgenogram of the chest. The heart, however, will be normal in size.

**Laboratory Examination**—An extensive replacement of the liver parenchyma has to occur before there is any significant measurable impairment of hepatic function (Paulson), and for this reason, most liver function tests are of little or no value in the diagnosis of primary carcinoma of the liver. The

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## CARCINOMA OF THE GALL BLADDER

### Anatomy

The gall bladder is normally attached directly to the inferior surface of the right lobe of the liver by loose areolar tissue. This attachment separates the quadrate lobe from the remainder of the right lobe. The gall bladder has a deep, medially directed neck, a body, and a free distal end, the fundus. The arterial supply to the gall bladder is derived directly from the cystic artery,

metrium, lung, and breast. Melanomas of the skin and eye also frequently metastasize to and considerably enlarge the liver. Particular attention, consequently, should be paid to the history of suspicious nevi or enucleations of the eye which might appear irrelevant in the history of the patient. An exploration of the abdomen may be necessary at times in order to establish a definite diagnosis.

*Cirrhosis* of the liver may be mistaken for carcinoma but the cirrhotic liver is usually small instead of large and a long history of gastrointestinal difficulties is usually given. In *hemochromatosis*, the liver may be indurated and nodular, and if sudden improvement of the diabetes (even hypoglycemic intervals) accompanied by fever, anemia, leucocytosis, and weight loss occurs the coexistence of a primary carcinoma of the liver should be strongly suspected.

If a tumor is localized to and apparently primary in the liver, it may be difficult to determine whether it is benign or malignant. A single, movable, nontender mass giving vague gastrointestinal disturbances in a patient in good general condition, is usually a benign lesion. However, if there are systemic symptoms with anemia, weight loss and hard, often multiple, tender masses, a malignant tumor is probably at hand. Roentgenologic study and an exploratory laparotomy may be necessary to establish a diagnosis.

### Treatment and Prognosis

Carcinoma of the liver can be cured only by a surgical excision and this is, of course, only possible when the lesion is so localized that it can be removed. The excision does not appreciably impair the functional capacity of the liver which has a tremendous reserve. Warvi (1945), in reviewing 223 cases of excisions for carcinoma of the liver, has emphasized that the most common cause of failure is incomplete excision and that the operative mortality is not high. Charache (1939) collected from the literature fourteen cases of surgical resections for carcinoma of the liver. Of these five of the patients were dead, one was lost to follow up and only five of the remaining eight patients were living one year after the operation. Only one of these lived over five years.

In a series of cases of carcinoma of the liver reported by Gustafson the average course from the first symptom to death was 32 months, the average duration being longer in the bile duct cell type of tumor than in the liver cell type. Wilbur has suggested that in patients with cirrhosis the development of hepatic carcinoma might be prevented by a diet rich in the components of the vitamin B complex.

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which lies between the gall bladder and hepatic surface. The venous drainage goes directly into the hepatic divisions of the portal vein.

**Lymphatics**—The lymphatics of the gall bladder, arising from the mucosa, travel through the muscular wall to empty into a subserous lymphatic network. The trunks empty into lymph nodes of the anterior border of the foramen of Winslow, in the lymph node of the neck of the gall bladder, and in the hepatic lymph node (Fig 476). These lymphatics have abundant anastomoses with the lymphatics of the liver.

### Incidence and Etiology

Of all carcinomas of the organs of digestion, cancer of the gall bladder stands fifth in incidence. It appears in women four times more commonly than it does in men, predominantly in the older age groups (80 per cent of the patients are over 50 years of age, and it is infrequently found in patients under 40).

Primary carcinoma of the gall bladder is found in approximately 1 per cent of the patients operated for a clinically diagnosed cholecystitis, when gallstones are present; the incidence of carcinoma is between 4 and 5 per cent (Jankelson). There is, however, considerable disagreement as to the relation of gallstones to carcinoma which may be condensed to three viewpoints: first, that the gallstones are a precursor of the carcinoma, second, that gallstones form because of the presence of carcinoma, and third, that an initial inflammation causes both the gallstones and carcinoma. Gallstones are certainly present in a high percentage of patients with carcinoma of the gall bladder; the reported figures ranging from 65 per cent (Judd) to 100 per cent (Janowski). Jankelson believes that stones follow rather than precede carcinoma. Papillomas of the gall bladder are rarely precursors of carcinoma, for in 500 cases reported by Phillips only one carcinoma questionably arose on this basis.

Until recently, experimental proof was lacking that stones or foreign bodies could cause carcinoma of the gall bladder (Burrows). Petrov and Krotkina, however, produced unequivocal carcinoma of the gall bladder in guinea pigs following the introduction of sterile hard foreign bodies into the gall bladders. In the five carcinomas produced, four developed distant metastases. They believe, therefore, that in the association of gall stones and cancer of the gall bladder, the role of the stones is primary.

### Pathology

**Gross and Microscopic Pathology**—About 80 per cent of the carcinomas of the gall bladder arise in the dome or neck and the other 20 per cent in the lateral walls. These tumors are of two varieties, epidermoid and adenocarcinoma. The epidermoid type of carcinoma is rare, frequently exists with stones, and undoubtedly occurs because of metaplasia of the epithelium which can at times be seen (Fig 477). Of the three varieties of the adenocarcinoma, the scirrhous type is the most common (approximately 55 per cent), is accompanied by considerable connective tissue, and invades contiguous structures rather quickly. The papillary type of adenocarcinoma (approximately 25 per cent) has a papillary overgrowth which tends to grow within the lumen and to form a

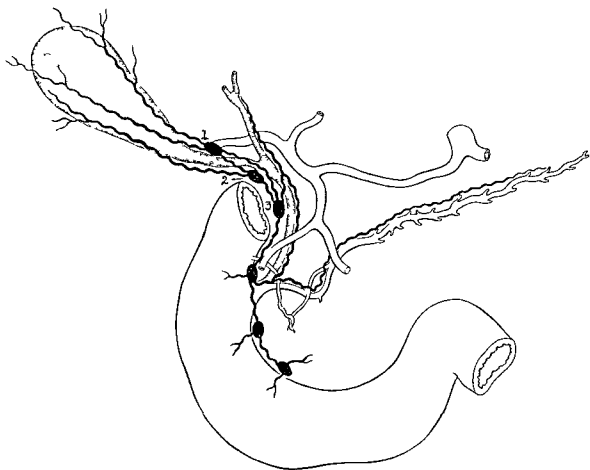


Fig 4 C—Schematic representation of the lymphatics of the gall bladder showing the pathways to 1 cystic node 2 node of anterior border of foramen of Winslow and 3 superior retropancreaticoduodenal node

can occur. Rarely the disease implicates the hepatic flexure or transverse portion of the colon. Peritoneal involvement is quite common, the gelatinous type of carcinoma sometimes implanting on the peritoneal surface and causing secondary invasion of the bowel. Fistulous communication may develop between the gall bladder, stomach, duodenum, and colon.

When tumor is present within the gall bladder infection often follows. This complication may cause empyema of the gall bladder, perforation, gangrene, generalized peritonitis, ascending suppurative cholangitis and liver abscesses (Liebowitz). Direct invasion of the gall bladder by carcinoma arising in the liver, bile ducts, stomach or pancreas can occur but metastatic lesions are rare.

A benign neoplasm of the gall bladder is rare and is found in only about 1 of every 100 surgically removed gall bladders. It is usually a polyp adenoma or a fibroma (Shepard).

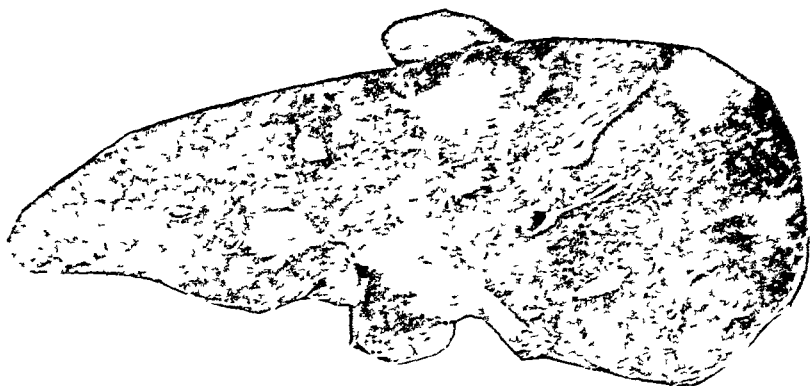


Fig. 478.—Local spread of a carcinoma of the gall bladder by means of the biliary duct system.

**MEASTATIC SPREAD**—A carcinoma of the gall bladder most frequently spreads by the lymphatics to involve the cystic and periportal nodes, then the nodes about the head of the pancreas and finally the retroperitoneal lymph nodes (incidence about 50 per cent). Distant metastases to the lungs, bones, suprarenal glands, spleen and other organs have been reported but are only infrequently encountered.

### Clinical Evolution

Carcinoma of the gall bladder has an insidious onset, eludes early diagnosis and is often recognized only at exploration or necropsy. The clinical picture depends, to a great extent, upon the location of the lesion, its extension, and metastases and on associated conditions related to infection, stones or pancreatitis.

A typical case is a woman about 60 years of age with a possible history of biliary colic and complaint of pain, steady and severe, of one or two months'

bulky, rather slowly growing tumor. It is frequently accompanied by necrosis and infection. The colloid or mucinous adenocarcinoma (15 per cent) tends to form large soft masses.



Fig 477—Epidermoid carcinoma of the gall bladder with local invasion of the surrounding structures associated with a single large gallstone.

Carcinoma of the gall bladder invades the liver fairly early in its evolution and may also directly extend into the extrahepatic ducts (Fig 478). Direct spread to the stomach and duodenum with even complete pyloric obstruction

if a carcinoma exists, the gall bladder does not fill with the dye. Kirklin reviewed sixteen cases of carcinoma of the gall bladder which had cholecystograms. Of these, fourteen showed no gall bladder shadow but seven revealed stones. The fifteenth had multiple stones and normal function, and the sixteenth had function with no stones. Tateika diagnosed a carcinoma of the gall bladder by cholecystogram when he observed a defect measuring more than 2 cm in diameter, having an irregular internal border. Kirklin, moreover, by means of cholecystograms, has accurately diagnosed papillomas and adenomas of the gall bladder. Laboratory tests of liver function are usually noncontributory.

**Differential Diagnosis**—*Cholecystitis* and *cholelithiasis* are invariably accompaniments of carcinoma of the gall bladder. In early carcinoma, it is impossible to be clinically sure that it coexists with these two conditions. Inflammatory complications with cholangitis or peritonitis may obscure the underlying neoplastic process. Carcinoma should be suspected, however, if previous signs and symptoms of cholelithiasis have been present or if there is a firm mass in the region of the gall bladder. A tumor of the gall bladder is not usually confused with the lesions of the periaampullary region or with stone in the common bile duct, for these conditions (in contrast to carcinoma) produce an intense jaundice and have other laboratory or roentgenologic findings to help differentiate them.

### Treatment

The only chance to cure a carcinoma of the gall bladder is by complete surgical removal. If the clinical diagnosis is obvious, then usually the patient is inoperable. For this reason Moynihan, Graham, and Finsterer advise prophylactic removal of all gall bladders containing stones. The incidence of carcinoma of the gall bladder in patients with gallstones is between 4 and 5 per cent, and the operative mortality of cholecystectomy according to Graham is only 1 to 3 per cent. He argues that the operation not only may eradicate an early carcinoma but evades the liability of gall bladder colic, infection, gangrene, or perforation. Jaguttis followed 114 cases of cholelithiasis which were treated conservatively ten to twenty-five years; thirty-eight of the patients died. Five of these thirty-eight developed carcinoma of the gall bladder, and thirteen died of cholecystic disease. Therefore, almost one-half of the deaths were due to cholelithiasis or its complications. This report does not take into account the disturbing symptomatology which probably accompanied cholelithiasis in many of the surviving patients. A cholecystectomy certainly seems indicated even if the supposition is accepted that stones do not cause cancer. If all gall bladders showing stones are treated by a cholecystectomy, an increased number of patients with early and therefore curable carcinomas of the gall bladder will be salvaged. Conversely, if the treatment of a carcinoma of the gall bladder is carried out only after the disease is clinically evident, the prognosis is invariably hopeless.

### Prognosis

The prognosis for carcinoma of the gall bladder is extremely poor. In most of the large reported series, only a very few patients live five years, the majority

duration, in the right upper quadrant, there may be nausea and vomiting also and she may or may not be jaundiced, the liver and the tumor may both be palpable (Lam)

About 70 per cent of the patients with carcinoma of the gall bladder have a long history of repeated gall bladder attacks. These attacks eventually change in character in so far as they are followed by a short period of pain, vomiting, epigastric distress, diarrhea belching, progressive weakness weight loss, or anorexia all appearing within a six month period (Mohardt). Just as in other gall bladder disease the pain caused by cancer radiates to the left upper or lower quadrants of the abdomen. As the tumor increases in size the pain becomes more frequent and persistent, and jaundice appears in about 60 per cent of the cases. This jaundice, obstructive in type, is caused by neoplastic involvement of the regional lymph nodes pressing on the extrahepatic ducts. Ascites may occur due to portal vein obstruction secondary to involved metastatic nodes.

With further progress of the disease, the tumor very frequently causes inflammatory complications which may result in cholangitis with high fever. At times a liver abscess may form and perforation of the gall bladder with terminal peritonitis is not unusual. The disease is terminated more frequently by these inflammatory complications than from a widespread metastatic process.

### Diagnosis

The diagnosis of an early carcinoma of the gall bladder is practically impossible. The frequent association of carcinoma and stones makes it imperative that any patient with stones (particularly a woman over 40) be examined carefully for evidence of carcinoma of the gall bladder. Usually symptoms and signs of cholecystitis and cholelithiasis are present. When the disease becomes advanced, the gall bladder becomes palpable firm and later in its evolution fixed. Early jaundice is seldom present. Clinical signs of weight loss and anemia are not apparent until the end.

In a group of seventy five patients reported on by Lichtenstein, fifty (or 67 per cent) had pain in either the right upper quadrant or the epigastrium. In twenty six (52 per cent of those with pain), this pain was present less than six months, and in thirty one (62 per cent of those with pain), it was present for less than a year. Weight loss occurred in forty three (or 57.3 per cent) and jaundice in forty one (or 54.7 per cent). The combined symptoms of pain weight loss and jaundice were present in fifteen of the seventy five patients. If the tumor originates in the fundus it may not give rise to symptoms until after dissemination has taken place, but on the other hand, if it arises in the neck cystic duct obstruction may occur early. The inflammatory complications occurring near the end of the evolution are often confusing.

**Röntgenologic Examination**—Carcinoma of the gall bladder is practically never diagnosed by roentgenograms alone. If barium meal or enema demonstrates a fistulous connection between the gall bladder and the stomach or colon, there is a strong possibility that carcinoma of the gall bladder exists. Two cases of this nature with a correct preoperative diagnosis were described by Spitznberg. Even a cholecystogram is useless as a diagnostic measure for

if a carcinoma exists, the gall bladder does not fill with the dye. Kirklin reviewed sixteen cases of carcinoma of the gall bladder which had cholecystograms. Of these, fourteen showed no gall bladder shadow but seven revealed stones. The fifteenth had multiple stones and normal function, and the sixteenth had function with no stones. Tateika diagnosed a carcinoma of the gall bladder by cholecystogram when he observed a defect measuring more than 2 cm in diameter, having an irregular internal border. Kirklin, moreover, by means of cholecystograms, has accurately diagnosed papillomas and adenomas of the gall bladder. Laboratory tests of liver function are usually noncontributory.

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### Prognosis

The prognosis for carcinoma of the gall bladder is extremely poor. In most of the large reported series, only a very few patients live five years, the majority

dying within a year of operation, and frequently the mortality rate is 100 per cent. In fifty four patients operated on reported by Vardheim, eight were alive at the end of five years, but the lesions in seven of these were well differentiated and limited to the mucosa and submucosa.

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## CAPCINOMA OF THE EXTRAHEPATIC DUCTS AND PEPIAMPULLARY REGION

### Anatomy

The extrahepatic bile ducts vary considerably in length, structure, course, and relation to one another, and it is difficult to distinguish the normal from the abnormal. The left and right hepatic ducts originate in the transverse fissure of the liver but unite at a 60 degree angle to form the common hepatic duct which courses backward, downward, and medially in the gallbladder fossa. The extrahepatic duct has an average length of 3.0 centimeters. This duct crosses the first part of the hepatic artery and the portal vein. At the point where the duct crosses the hilus it overlies the medial portion of the portal vein and the hepatic artery passes at the left of the duct. The extra-



duct is a continuation of the neck of the gall bladder and averages 4 cm in length. The upper proximal portion has a redundant lining which is arranged in spiral folds to form Heister's valve. The distal portion of the cystic duct extends downward to join the hepatic duct. This point of union may be of three types: the parallel type present in 36 per cent of the cases, usually deep behind the duodenum, the spiral type seen posteriorly to the left in 28 per cent, and the angular type present in 36 per cent, usually on the right of the hepatic duct (Nuboei). The common bile duct averages 7 cm in length and can be divided into three portions. The suprapancreatic portion lies behind the duodenum and naturally varies in length according to the point of confluence between the cystic and hepatic ducts. If this point of confluence is low, the suprapancreatic portion is absent. The duct descends to the right of the hepatic artery anterior to the portal vein and along the lesser omentum at its right margin. The second or pancreatic portion of the common bile duct is within a groove or tunnel in the posterior surface of the pancreas where it enters the descending duodenum. This portion is 3 to 5 cm in length and is separated

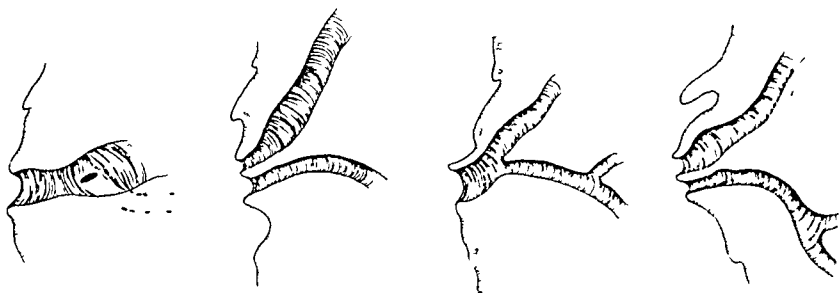


Fig. 179—Four anatomic types of ampulla of Vater (according to Lettelle)

from the vena cava by a thin segment of pancreas or by connective tissue. The third portion of the common bile duct is the ampulla. A true ampulla in the sense of a pouch lying within the papilla is present in only about one third of the cases (Lettelle). Besides the true ampulla (type 1), there are three other variations: the pancreatic duct empties into the choledochus at some distance from the duodenal wall without formation of a true ampulla (type 2), the two ducts open side by side on the surface of the intestine without the formation of a papilla (type 3), or finally, the two ducts form a prominent papilla in the duodenal lumen but remain separate (type 4).

**Lymphatics**—The lymphatics of the cystic, hepatic, and common bile ducts arise from a mucous network which communicates directly with the network on the external surface of the ducts. The lymphatic collecting trunks of the cystic duct empty into the cystic node and into the node on the anterior border of the foramen of Winslow. The lymphatics of the hepatic duct empty into the node of the foramen of Winslow and a superior retropancreatoduodenal node. The collecting trunks of the common bile duct are drained by the lymph node of the foramen of Winslow and the posterior pancreatoduodenal lymph nodes.

dying within a year of operation and frequently the mortality rate is 100 per cent. In fifty-four patients operated on reported by Adheim eight were alive at the end of five years, but the lesions in seven of these were well differentiated and limited to the mucosa and submucosa.

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## CARCINOMA OF THE EXTRAHEPATIC DUCTS AND PERIAMPULLARY REGION

### Anatomy

The extrahepatic bile duct varies considerably in length, structure, course, and relation to its contents, and it is difficult to distinguish the normal from the abnormal. The left and right hepatic ducts originate in the transverse fissure of the liver, unite at a 90 degree angle to form the common hepatic duct which extends downward and laterally in the lesser omentum to the gallbladder. The common hepatic duct has an average length of 3 centimeters. This distance is the distance of the hepatic artery and the portal vein. At the point where the duct crosses the hepatic artery, the duct is slightly to the right of the hepatic artery, and the hepatic artery is to the left of the duct. The extra-

the ampulla or very rarely from aberrant pancreas or even Brunner's glands. The first three are by far the most common but it should be remembered that carcinoma which arises from the head of the pancreas may simulate a primary tumor of the extrahepatic ducts. The number of tumors of the periaampullary region in which the exact site of origin can be ascertained remains very small inasmuch as so very few cases have complete post-mortem examinations. Lieber,

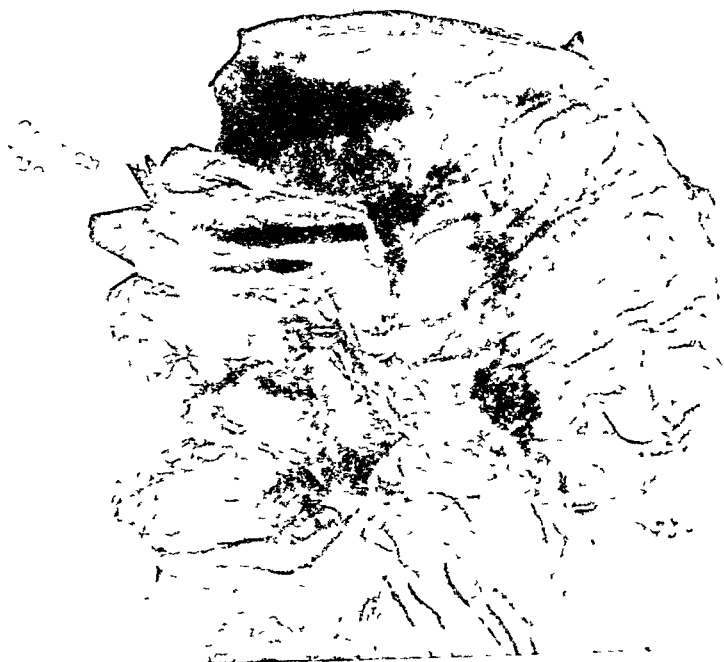


Fig 480—Carcinoma of the ampulla of Vater (Courtesy of Dr. A. P. Stout, Department of Surgical Pathology, Columbia University, New York, N. Y.)

in 1939 analyzed all the reported tumors from the periaampullary region but was forced to reject many of them because of inadequate data. He finally grouped them as follows:

TUMORS OF THE PERIAAMPULLARY REGION	NUMBER OF CASES
Primary carcinoma of the ampulla	1
Primary carcinoma of the terminal duct of Wirsung	3
Primary carcinoma of the terminal common bile duct	7
Primary carcinoma of the intestinal mucous membrane covering papilla of Vater	
Primary carcinoma involving all the structures detailed in the first four groups	182
Primary carcinoma involving all structures comprising the papilla except tumors arising from the intestinal mucous membrane	2

Carcinomas of the extrahepatic ducts may be either papillary or flat and ulcerated. They may be localized or diffuse. The grouping of Stewart's cases

The lymphatics of the ampulla of Vater anastomose with those of the duodenum and the main pancreatic duct and of necessity, therefore with the lymphatics of the pancreas

### Incidence

Malignant tumors which develop in the extrahepatic ducts are relatively few in number. The ratio of carcinoma of the head of the pancreas to carcinoma of the extrahepatic ducts is about 4 to 1. In 109 verified cases reported by Hanson eighty three arose from the pancreas and twenty six from the extrahepatic ducts of these twenty six eighteen were from the ampullary region. The ratio of carcinoma of the extrahepatic duct to carcinoma of the gall bladder is about 1 to 7. In 312 cases of carcinoma of the gall bladder and extrahepatic ducts collected by Judd 100 arose from the extrahepatic biliary ducts. Cancer of the extrahepatic duct is found twice as frequently in males as in females. Of 104 cases of cancer of the extrahepatic ducts (exclusive of the periampullary region) collected by Stewart seventy three were in men and thirty one in women. These tumors are associated with stones in approximately 20 per cent of the cases.

### Pathology

**Gross Pathology.** Cancer of the extrahepatic ducts may be specifically located in the cystic duct, the hepatic duct, in the confluence formed by the cystic and hepatic ducts, or in the common bile duct.

Rolleston found the following distribution in 124 cases of carcinoma of the biliary tract:

Common bile duct	
Lower end	1
Middle	11
Junction of common bile duct with common hepatic duct	2
Common hepatic duct	18
Upper end of hepatic duct	
Lower end	1
In cystic duct at junction of bile duct	1
	50

It should be noted that the highest proportion of these cases occurred at the lower end of the common bile duct and at the confluence of the cystic and hepatic ducts. Scott (1940) critically analyzed all the cases of carcinoma of the extrahepatic ducts that had been reported and found thirty five arising from the hepatic duct, forty eight from the confluence of the extrahepatic duct, and twenty six from the common bile duct. He pointed out that it was often very difficult to establish with certainty the site of origin of these tumors when the pathologic picture was far advanced. He collected 104 cases of carcinoma of the extrahepatic ducts of the cystic duct, 18 of the common bile duct, and 11 of the hepatic duct. He found that the pathologic picture of carcinoma of the lower third of the common bile duct

is the same as that of the common bile duct. The carcinoma of the lower third of the common bile duct is the same as that of the common bile duct. The carcinoma of the lower third of the common bile duct is the same as that of the common bile duct.

Confirmation of the slow growth of these tumors has been obtained from observations at exploratory operations and ultimate post-mortem examination. Invariably there is partial or complete obstruction of the common bile duct with consequent dilatation of the duct. When the duct is completely obstructed,



Fig. 452 —Adenocarcinoma of the terminal third of the common bile duct for which a one stage pancreatoduodenectomy was performed

it usually measures between 5 and 8 cm in diameter. This obstruction is due to neoplastic annular constriction (most common cause), pressure of the primary duodenal tumor, secondary invasion of the pancreas after metastases to regional nodes or to concomitant biliary calculi.

is shown in Table XXVI. The same is true of the tumors which arise in the periampullary region. All of these tumors spread to invade contiguous tissue. The carcinomas arising from the head of the pancreas or from the duct of Wirsung may invade the terminal third of the common bile duct, but the reverse does not often take place. In 117 tumors arising from the common bile duct, there was secondary invasion in only thirty four (Lieber, 1939). The tumors arising from the hepatic ducts quickly invade the liver or extend farther down



Fig. 481.—Photomicrograph of the gross specimen illustrated in Fig. 480 showing the local extent of the tumor (very low power enlargement). (Courtesy of Dr. A. E. Stout, Department of Surgical Pathology, Columbia University, New York, N. Y.)

the ducts. The carcinoma arising at or below the confluence blocks off ducts and causes dilatation of the common bile duct and gall bladder.

TABLE XXVI. CARCINOMA OF THE EXTRAHEPATIC DUCTS. GROSS CHARACTERISTICS OF NEOPLASMS AND FREQUENCY OF METASTASIS.

(From Stewart, H. L. and Lieber, M. M. Arch. Surg. 1940.)

LOCATION	NUMBER OF CASES	FORM	METASTASES
Hepatic duct	35	Local tumor 75%—diffuse 25%	48%
At the confluence	48	Local growth 56%—diffuse 44%	46%
Common bile duct	21	Local growth 57%—diffuse 43%	52%

character of the cells. In fact some workers have thought that they could distinguish tumors having primary origin from the duct of Wirsung or head of the pancreas from those arising from the terminal third of the common bile duct, but this can seldom be done.

### Clinical Evolution

One of the first signs of a carcinoma of the common bile duct or of the ampulla of Vater is jaundice (Cattell). It was the first symptom in 136 of 222 patients (Lieber, 1939) and was eventually present in all but four patients. The jaundice accompanying carcinoma of the ampulla, although slowly progressive, often fluctuates because of ulceration of the papilla. It is also true that ulceration of the duodenum may cause bleeding into the gastrointestinal tract.

Pain is frequently a symptom of the disease. Table XXVII lists the frequency of symptoms and signs found by Cooper and Lieber. The longer the duration of obstructive jaundice, the greater the degree of liver damage which may lead to hemorrhage and cause death. Cholangitis and other local inflammatory conditions are often the cause of death, whereas widespread metastases are rarely the cause.

TABLE XXVII RELATIVE FREQUENCY OF SYMPTOMS AND SIGNS IN CARCINOMA OF EXTRAHEPATIC DUCTS  
(From Hyde, L., and Young, L. L. New England J. Med., 1910)

SYMPTOM OR SIGN	COOPER (%)	LIEBER AND CO. WORKERS (%)
Jaundice	95	98
Abdominal pain	86	59
Weight loss	78	
Anorexia	71	
Vomiting	36	58
Diarrhea	21	
Palpable gall bladder	50	50
Enlarged liver	86	78
Occult blood in stool	82	
Duodenal defect in gastrointestinal series	90	32

### Diagnosis

Tumors of the extrahepatic ducts are seldom diagnosed because they are seldom even considered. Only 39 of 222 cases were accurately diagnosed clinically, and the correct diagnosis was obtained in only 83 of the 122 cases in which exploration was carried out (Lieber, 1939). In sixty-two cases, one or more diagnoses were made: the most common was carcinoma of the head of the pancreas (twenty-five), calculus cholecystitis (fourteen), calculus cholecystitis (ten), and obstruction of the bile ducts (twelve).

*Clinical Examination*—Jaundice is invariably present with tumors arising from the extrahepatic ducts and perampullary region. It is very frequently the first sign of a tumor of the ampulla, and it may wax and wane due to ulceration. In neoplastic obstruction of the common bile duct, however, jaundice appears slowly and only gradually deepens to become intense. The gall bladder is frequently palpable and the liver is often enlarged in all of these patients.

Along with these changes there may be inflammatory lesions which, particularly in the periampullary region, may be accompanied by pancreatitis which in turn is sometimes associated with fat necroses. With obstruction of the duct of Wirsung, there may be cystic dilatation of all its ramifications giving the pancreas a firm, indurated consistency and causing diminution of function. There also may be an ascending infection of the biliary tree with cholangitis or empyema of the gall bladder. The liver is usually enlarged and the surface smooth, but occasionally it may be finely or coarsely nodular. The cut surface is deeply bile stained and there may be considerable distention of the intrahepatic ducts.

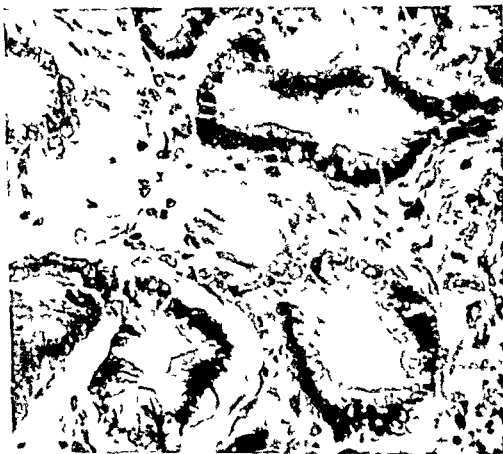


Fig. 483—Photomicrograph of the specimen illustrated in Fig. 482 showing the well differentiated character of the tumor (moderate enlargement).

**METASTATIC SPREAD**—Carcinomas of the extrahepatic ducts metastasize rather early to the regional lymph nodes. In 182 neoplasms (carcinoma involving all the structures comprising the papilla of Vater) reported by Lieber (1939), metastases occurred in 43 per cent. In 103 patients with this group of carcinomas of the periampullary region, the growth was nonulcerated and limited to the papilla. The carcinomas arising from the ampulla of Vater and from the intestinal mucosa overlying the ampulla tend to metastasize late.

**Microscopic Pathology**—All of these tumors are adenocarcinomas. It would be very helpful if the primary origin could be identified by the histologic



80 per cent of the patients with common duct stone have a contracted, atrophic, functionless gall bladder, and when evidence of intermittent block is also apparent, bile will be found in the stool and urobilinogen in the urine, particularly if frequent tests are made. There are a few patients in the older age group who give no history of pain suggesting calculi, and a preoperative diagnosis of carcinoma of the head of the pancreas is made. *Stones in the ampulla* give approximately the same signs and symptoms as stones in the common bile duct. In 160 cases reviewed by Judd, 75 per cent of the patients were between 40 and 60 years of age, and seventy-two of these had had one or more previous operations. The usual story was that of repeated attacks of paroxysms of pain followed by chills, fever, jaundice, and residual tenderness. Pain (mild or severe) was present in 155 of the 160 patients. In 73 per cent of the patients, jaundice appeared for a few days or a few weeks (only thirty-seven escaped developing jaundice altogether). This jaundice gave a direct van den Bergh reaction, and in 83 per cent bile could be found in the duodenum by using the Rehfuss tube. At times the laboratory tests show absolute obstruction, but if these tests are repeated, evidence of intermittent obstruction will be found. Sepsis as manifested by chills and fever was present in 51 per cent of the patients. In 110, stones in the gall bladder were also present.

The presence or absence of a palpable gall bladder is very important in deciding whether the lesion is benign or malignant. A high percentage of the malignant neoplasms of the periaampullary region cause a dilated gall bladder while conversely an extremely small proportion of benign obstructive lesions are accompanied by enlargement of the gall bladder. However, even a dilated gall bladder may not be felt if there is obesity or if a large right lobe of the liver is overlying it or because of lack of cooperation on the part of the patient.

After there is no doubt that the lesion which is causing the jaundice is malignant, its origin must then be determined. Tumors of the extrahepatic ducts are relatively few compared with the number arising from the head of the pancreas and gall bladder. In *carcinoma of the pancreas* the weight loss, anemia, and other symptoms are usually followed by jaundice, while in carcinoma of the common bile duct or ampulla, jaundice is one of the first symptoms. The jaundice accompanying a pancreatic tumor is of a greater intensity than the jaundice of ampullary and bile duct tumors. It is also progressive and unrelenting. Because of the ulceration which may occur in carcinomas of the terminal third of the common bile duct, and particularly in those arising from the ampulla and from the intestinal epithelium overlying the ampulla, bleeding into the gastrointestinal tract can occur. Usually this bleeding is minimal in amount and gross hemorrhages do not occur. It is also possible, however, for carcinoma of the head of the pancreas to ulcerate the intestinal mucosa. Bile may be intermittently present in the feces in carcinoma of the terminal third of the common bile duct and carcinoma of the ampulla because of intermittent alleviation of the obstruction due to necrosis of the tumor. By contrast, the carcinoma of the head of the pancreas never produces any bile in the feces. Pancreatic enzymes are invariably absent in carcinoma of the head of the pancreas but may be present in carcinoma of the terminal third of the common bile duct or ampulla (Table XXIX).

The gall bladder may not be felt however, if there is poor cooperation on the part of the patient, if the abdominal wall is very thick or if the patient is obese.

### Röntgenologic Examination —

*Röntgenologic studies* of the gall bladder and gastrointestinal tract may show failure of the gall bladder to fill and may, upon occasion, show a duodenal defect. A gastrointestinal series was done on forty nine patients and in sixteen a lesion of the papilla was present recognizable by a continued duodenal deformity most often in the second portion (Lieber, 1939).

**Laboratory Examination**—Laboratory procedures (as detailed under *Carcinoma of the Head of the Pancreas*) are also indicated here. The investigations are directed to finding out whether or not complete biliary obstruction is present. Frequent observations of duodenal contents are necessary to determine the presence or absence of bile, pancreatic secretions and blood.

**Differential Diagnosis**—The patient with a carcinoma of the extrahepatic ducts or ampulla invariably has jaundice. Therefore differentiation has to be made from other conditions which give jaundice. In the first place non-obstructive forms of jaundice have to be ruled out, but usually the cause is obvious. *Toxic hepatitis* may at times be confusing and the obstruction temporarily complete. However this inflammatory process generally appears in young individuals the jaundice tends to clear, and, with adequate laboratory tests the obstruction is proved incomplete.

Carter reported on a series of 3607 patients with disease of the liver and biliary tract admitted to the New York Postgraduate Hospital between 1916 and 1936 (Table XXVIII). From the statistical standpoint the chances are high that when obstructive jaundice occurs it results from a benign cause such as a stone rather than to a malignant neoplasm.

TABLE XXVIII. COMPARATIVE INCIDENCE OF JAUNDICE AND AGE INCIDENCE OF DIFFERENT OBSTRUCTIVE BILIARY CONDITIONS  
(From Carter, P. F., Greene, C. H. and Twiss, J. P., *Diagnosis and Management of Disease of the Biliary Tract*, Philadelphia 1939 Lea & Febiger.)

	NUMBER OF OPERATIVE CASES	NUMBER OF CASES WITH JAUNDICE	AGE
Cholelithiasis	1,346	98 (22%)	50 to 60
Acute cystitis cholelithiasis	35	103 (29%)	40 to 60
Cholelithiasis (stone in the common duct)	105	63 (62%)	40 to 60
Carcinoma of the pancreas	94	61 (65%)	50 to 60
Carcinoma of the gall bladder	4	19 (41%)	60 to 70

Of the benign conditions the most difficult one to differentiate is *common duct stone*. The associated symptoms are biliary colic, jaundice, chills and fever usually in this order. Dark urine and acholic stools usually follow the attack. Colic frequently indicates the passing of a stone from the cystic duct into the common duct. The jaundice which follows may wane as the stone passes into the duodenum or into a true ampulla. It is rare that complete obstructive jaundice is present. It is usually intermittent. In a series of 106 cases reported by Jordan all of the patients had symptoms of recurrent colic for variable periods of time but fourteen (or 13 per cent) never had any jaundice at all. About

Movnihan succinctly states "No one living is infallible in the differential diagnosis of obstructive jaundice, the diagnosis is always difficult" There are fairly frequently, no absolute differentiating signs

### Treatment

Carcinoma arising in the hepatic duct is practically never operable because of direct extension into the liver. Carcinoma of the terminal third of the common bile duct is also seldom operable, Stewart (1940) was able to collect only three surgically treated cases. Carcinomas of the perampullary region are more suitable for surgical treatment because they tend to remain localized. At the time of exploration, however, the liver, head of the pancreas, and regional lymph nodes should be carefully examined. Frozen section of an enlarged distant lymph node or the liver may show metastatic disease and any further surgery is contraindicated. If the diagnosis is still questionable after this limited exploration, then a duodenectomy should be done. A papillary tumor may be biopsied and a frozen section done but it should be remembered that these tumors are of low malignancy and a biopsy of the superficial portion may give an entirely erroneous impression of their potentialities (Child).

If carcinoma is proved a radical one-stage pancreatoduodenectomy rather than a local resection should be done. Of ninety-eight patients in whom local excision with transplantation of the common bile duct and pancreatic duct was done, there was an immediate 20 per cent operative mortality (Hunt). Only five patients were alive at the end of four years. This operation should therefore be considered palliative rather than curative. In a recent series of fifty-one cases of pancreatoduodenal tumors reported by Cattell, only seventeen were eligible for a radical resection. It is interesting that only three of these operable cases arose from the head of the pancreas, although carcinoma of the pancreas is about four times as frequent in incidence as perampullary cancer.

### Prognosis

The prognosis of carcinoma of the hepatic duct is invariably poor. Stewart found only one patient with carcinoma of the lower segment of the common bile duct living and well ten months following operation. In the ninety-eight cases of carcinoma of the perampullary region compiled by Hunt, five of the patients lived from four to twenty-two years following operation. Of eighty-six cases of carcinoma of the ampulla of Vater and perampullary portion of the duodenum, thirty-six of the patients were living and well, but only ten had gone three years or longer. Of the twenty-six who were known to have died of disease, sixteen died within the first year, and only two showed evidence of recurrence after thirty months. In view of these figures, it seems logical to conclude that if recurrence does not appear within three years of operation, the chances of its eventual occurrence are rather small.

In forty-seven untreated patients reported by Outerbridge, the average time from onset of symptoms to death was a little over seven months, and in 50 per cent of the patients the duration of life was less than six months. In 100 inadequately treated patients, 97 survived for an average of six months from the onset of the disease (Laeber, 1939).

TABLE XXX DIFFERENTIAL CHARACTER OF BENIGN AND MALIGNANT LESIONS INVOLVING BILIARY TRACT PERIAMPULLARY REGION, AND HEAD OF PANCREAS

Age Sex Character of jaundice	CARCINOMA OF THE GALL BLADDER	CARCINOMA OF THE PERIAMPULLARY REGION	CARCINOMA OF THE HEAD OF THE PANCREAS	CHOLELITHIASIS	STONE IN THE COMMON BILE DUCT
	30 to 70 (80% over 50) Females 1 to 1 Usually earlier late	30 (1 each age) Males about 1 to 1 Usually first symptom tends to be incomplete	10 (1 each age) Males 3 to 1 Other symptoms precede progression to high level, obstruction complete	10 to 30 Females 4 to 1 Follows colic in high percentage tends to be incomplete	40 to 60 Females 2 to 1 Follows colic in high percentage tends to be incomplete
Percentage with jaundice	About 80%	About 90%	About 70%	About 20%	About 70%
Percentage with pain	About 60%	About 60%	About 80%	High	About 70% have real colic 20% have slight pain
Cholitic gall bladder	About 80%	Common bile duct in variably dilated	About 60%	Less than 5%	Less than 5%
Blood in the stools	Internally never	About 80%	Less than 5%	Practically never	Less than 5%
Roentgenologic findings <sup>1,2,4</sup>	Nonvisualization	Ulceration continued duodenal deformity	Widening of duodenal curve, invasion of duodenum invasion of stomach	Failure to visualize tons seen in 10%	Failure to visualize

## Chapter XI

### CANCER OF THE GENITOURINARY TRACT

#### CANCER OF THE KIDNEY

##### Anatomy

The kidneys are paired organs situated on both sides of the midline in the posterior abdomen at a level between the eleventh rib and the third lumbar transverse process. The left kidney is usually situated 2 cm lower. The kidneys assume a slightly oblique position and present an anterolateral and a posteromedial surface. The posterior relations are fairly constant on both sides formed by the psoas major, the quadratus lumborum, the diaphragm, and transversus abdominis muscles with the overlying twelfth dorsal, ileohypogastric, and ileo-inguinal nerves. Anteriorly the kidneys are in direct relationship with the suprarenal gland at their superior pole. The right kidney is in relation with the descending portion of the duodenum, the peritoneal cavity, the hepatic flexure of the colon, and the right lobe of the liver. The left kidney is anteriorly in relationship with the tail of the pancreas and with the posterior wall of the stomach through the omental bursa.

Both kidneys are surrounded by a fibrous capsule. The kidney in its capsule and the perinephric fat are enveloped by Gerota's fascia or renal fascia which arises from the transversalis fascia and divides into a posterior layer (fascia of Zuckerkindl), which attaches medially to the vertebral bodies, and a thinner anterior layer (fascia of Toldt), which extends beyond the midline to the opposite side. The fibrous envelope of the kidney is only open medially and inferiorly.

**Lymphatics**—The lymphatics of the kidney parenchyma and those of the fibrous capsule are continuous but they do not communicate with those of the adipose tissue. The lymphatics of the parenchyma are abundant, travel along the blood vessels, and from the cortical and medullary areas drain toward the base of the pyramids. At this point they unite and follow the blood vessels along the surface of the pyramids until they reach the pedicle, where they divide into three main trunks (Rouvière), depending on whether they are located in front, between, or behind the renal vessels.

1. The *anterior trunks* drain the anterior half of the kidney and terminate in the lateroaortic nodes between the renal and inferior mesenteric arteries. On the left side, the highest trunks may empty into a node situated at the junction of the left renal and suprarenal veins and into a node located at the point where the left spermatic vein drains into the renal vein. At times they may also drain into a node lying below the termination of the renal vein and into a precaval lymph node.

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2 The *middle trunks* of the right kidney usually terminate in the right lateroaortic node. On the left side they end in a node which is near the junction of the supracrenal and renal veins or in a lateroaortic node.

3 The *posterior trunks* originating from the posterior half of the kidney terminate, in the right side, in nodes which are located behind the inferior vena cava along the right border of the aorta, between the renal artery and the inferior mesenteric artery. On the left side the posterior trunks empty into the lateroaortic nodes near the origin of the renal artery.

The lymphatics of the *renal pelvis* are drained by the lateroaortic nodes which lie near the origin of the corresponding renal artery and the termination of the aorta and also into common iliac, hypogastric, and external iliac nodes.

### Incidence and Etiology

Approximately 99 per cent of all solid renal tumors are malignant in nature and about 80 per cent of these are adenocarcinomas. *Adenocarcinomas* of the kidney are usually encountered in men between the ages of 46 and 55, and in women a decade earlier. They occur more frequently in men, in a series of 402 cases, 227 were males and 175 females (Albarrán).

*Neoplasms of the kidney pelvis* make up only 5 to 10 per cent of all renal tumors. In a series of 585 kidney tumors collected by Albarrán, 42 originated in the pelvis. The ratio of these tumors to adenocarcinomas is about 1 to 14 (Braasch). The ulcerating epidermoid carcinoma arising from the pelvis has a suggestive etiology. Of 57 cases of ulcerating carcinoma reviewed by Gilbert, there were associated calculi and infection in thirty instances.

Wilms' tumors constitute about 6 per cent of all kidney tumors. They develop in the very young age group, about 80 per cent of them appearing in children under 7 and very few after 15 years of age (Table XXX).

TABLE XXX AGE DISTRIBUTION IN 165 CASES OF WILMS' TUMOR  
(From Albarrán, J., and Imbert, L. Les tumeurs du rein, Paris, 1903, Masson & Cie)

AGE IN YEARS	CASES	PERCENTAGE
0 to 3	89	54
4 to 6	42	25
7 to 9	21	13
10 to 12	7	4
13 to 15	6	4
Total	165	

### Pathology

**Gross and Microscopic Pathology**—Adenocarcinomas of the kidney are often found unexpectedly at necropsy, usually in kidneys which show evidence of previous disease. Mintz collected sixty-one kidneys containing 69 circumscribed lesions, the majority of which were less than 5 cm in diameter. There were only eleven without evidence of pre-existing renal disease. Seven were so-called fetal adenomas, forty-seven were papillary cystadenomas, and seven were adrenal rests. These small circumscribed cortical lesions were well de-

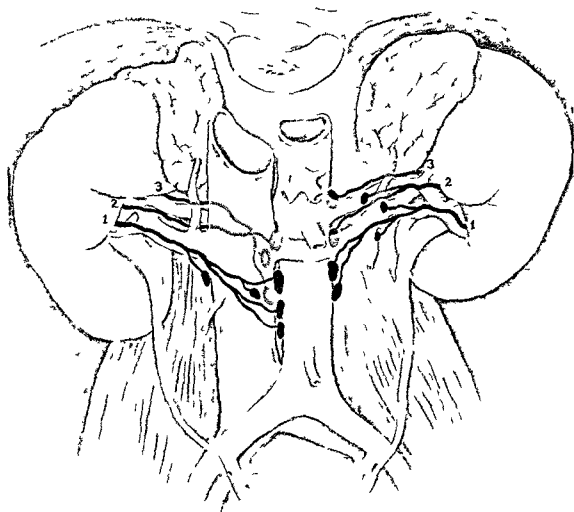


Fig 484—Anatomic sketch of the lymphatics of the kidneys showing 1 anterior trunks 2 middle trunks 3 posterior trunk (After Rouvière)



and individual acini are regular in appearance. Frequently the papillary-cell type of adenocarcinoma with granular cytoplasm is replaced in a few areas by large cells with foamy cytoplasm (Fig 486). These tumors can be divided into three microscopic variants designated as papillary diffuse, granular-cell, or clear-cell types. Multiple or large sections frequently reveal transitions and variations of all forms in the same tumor (Gottesman), and it is therefore logical to designate them all simply as adenocarcinomas of the kidney. They undoubtedly arise from renal tubules, and like renal tubules they may show hyaline droplets and a tendency to phagocytosis of broken-down blood pigment (Schiller).

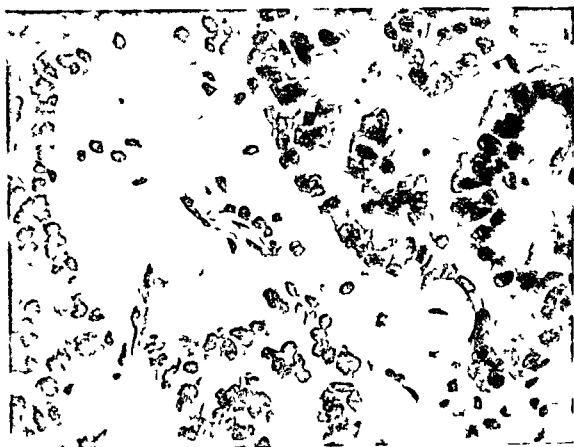


Fig 486—Photomicrograph of an adenocarcinoma of the kidney showing small areas in which the tumor cells have a foamy cytoplasm (high-power enlargement)

The transition point between *benign papilloma* and *papillary carcinoma* of the kidney pelvis is indefinite, and a high proportion of so-called papillomas of the kidney pelvis are, in a sense, malignant. They have a tendency to recur and from this viewpoint are analogous to the papillomas of the urinary bladder. Papillary carcinomas of the kidney pelvis form soft red or gray mammillated masses with smooth glistening surfaces, as if covered by mucus. The tumor is made up of arborescent ramifying papillary masses, and it sometimes resembles small pedunculated polyps with irregular surfaces (Fig 487). Surrounding the main tumor there are often smaller masses which may represent direct invasion of the ureter by the papillomatous neoplasm. Tumor is also frequently present in the upper and lower thirds of the ureter but the midportion may be free. These papillary tumors are not associated with leucoplakia, stones, or infection. Local recurrences after excision are frequent, but distant metastases are relatively uncommon.

Carcinomas of the kidney pelvis have the notorious quality of being accompanied by satellite lesions in the ureter and also in the opposite kidney pelvis or ureter. It is debatable whether this multiplicity on the same side is due to

lineated, were often homogeneous light yellow in color, and created a slight bulge in the overlying capsule of the kidney. The differentiation of adenoma and carcinoma cannot be made grossly.

The *adenocarcinomas* vary in size but as a general rule they usually do not reach the huge size of the Wilms tumor. These tumors have been designated as *hypernephromas* a name which specifies neither origin nor structure. Rarely they are bilateral (Forsythe). In forty six cases in which the point of departure



Fig 485.—Well delineated adenocarcinoma of the superior pole of the kidney with areas of hemorrhage.

was known twenty five were in the superior portion nineteen in the inferior portion and two in the midportion of the kidney (Albarran). The infiltrating type without enlargement of the kidney is rare. Adenocarcinomas are well circumscribed even when large and tend to grow toward the medullary portion of the kidney and its pelvis. On section they are usually bright yellow in color and hemorrhage and necrosis are common (Fig 485).

Microscopically it may be sometimes also impossible to determine if a tumor is an adenoma or an adenocarcinoma for encapsulation is often present in both

of the *ulcerating epidermoid carcinoma* arising from the pelvis of the kidney is a rare tumor commonly associated with nephrolithiasis and concomitant pyelonephritis.

The *Wilms' tumor* or *nephroblastoma* probably arises from embryonic nephrogenic tissue and represents a neoplastic exaggeration of the normal developmental process occurring in the blastemata of the renal cortex in late fetal life or in the first few months after birth (Gosch and Terz). Of nineteen cases in which the point of origin was known, twelve occupied the inferior pole, four the superior pole, and three the midportion of the kidney (Albarran). The tumor is usually well circumscribed, lobulated, and large (over 250 Gm.). It has a definite connective-tissue capsule which is continuous with that of the kidney. Because of the tendency of the tumor to remain confined, often reaching a large size before breaking through it. As the neoplasm dissects the capsule, its surface becomes lobulated and nodular. The cross-section of the tumor usually shows a gray or pinkish-tan, homogeneous, but hemorrhagic and necrotic, color. The consistency varies with the amount of cartilage and connective tissue present. The normal renal substance is often atrophied because of pressure.

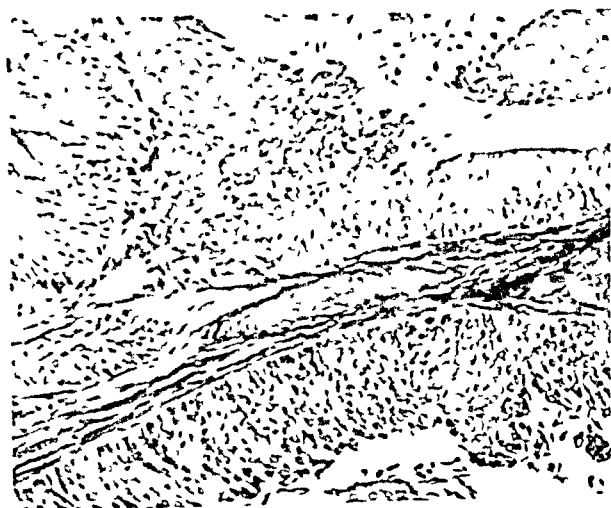


FIG. 488.—Malignant papillary tumor of the kidney pelvis (moderate enlargement)

At necropsy Wilms' tumors are often huge and attached to the contiguous organs by inflammatory or neoplastic adhesions. They spread by continuity toward the pelvis with invasion of the renal veins and rarely of the vena cava (Messinger). When the tumor has penetrated the capsule it may cause rupture and perineal extension. Adrenal invasion is most common in Wilms' tumors which arise in the superior portion of the kidney. Infrequently the tumor may directly invade the small bowel, large bowel, liver, or vertebrae.

implantation or is merely a reflection of an increased tendency of the mucous membrane of the genitourinary tract to form this type of tumor. We feel that probably it is caused by a malignant tendency of the epithelium similar to the tendency of the mucosa of the large bowel to produce multiple polyps and adenocarcinomas. Further supportive evidence lies in the fact that solitary papillary tumors of the ureters are rare. Kimball reported seventy-four kidney tumors involving more than one portion of the urinary tract.



Fig. 457.—Papillary carcinoma of the kidney pelvis. The first symptom was profuse hematuria.

Microscopic examination shows the central portion of the tumor made up of a connective tissue axis continuous with the submucosal tissue of the pelvis or ureter and there may be small strands of smooth muscle at the base. The epithelium is transitional in type, and the cellular characteristics are similar to papillary carcinomas of the bladder. It is often difficult to say which one of these tumors is benign the error of calling them benign being more common than the reverse (Fig. 488). Kidney tumors, unlike the ulcerating squamous carcinomas of the pelvis are usually not associated with infection. The firm

### Clinical Evolution

The evolution of the various types of kidney tumors varies considerably. *Adenocarcinomas* of the kidney arise within the parenchyma and do not give any signs or symptoms unless it is hematuria, which is the most common presenting symptom. In 368 cases reported by Judd, hematuria occurred as a *first symptom* in 43.8 per cent of the patients (60 per cent, Albarrán), pain in 37.3 per cent (30 per cent, Albarrán), and tumor in 13.6 per cent, during the evolution of the disease, hematuria developed in 69 per cent of the patients (80 per cent, Albarrán). Pain occurs during the course of the disease in about 80 per cent of the patients. With increase in the size of the tumor, a mass can sometimes be felt.

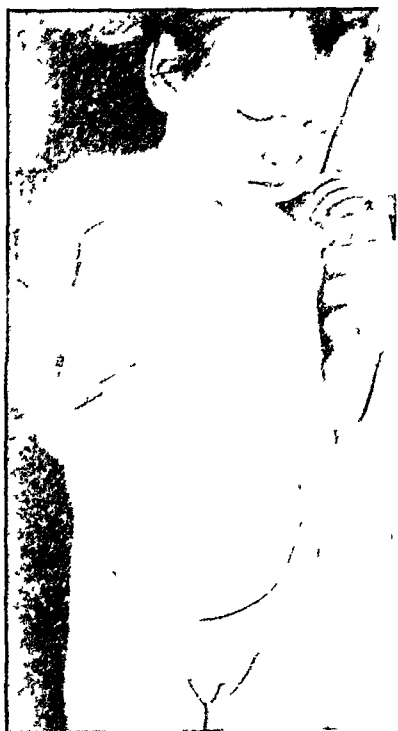


Fig. 491.—Wilms' tumor in a child 3 years of age. The outline indicates the extent of the palpable tumor. Note excellent general condition of the patient.

Blood clots may form, causing severe spasmodic pain as they pass down the ureter. Rather commonly (about 15 per cent) the first symptoms are due to bone or soft tissue metastases. As the disease disseminates, anemia, cough, and pleural pain may occur. Metastases to the brain are not unusual in the terminal stages. Low-grade fever may accompany the tumor, disappear with its surgical removal, and reappear with a recurrence. It is not unreasonable to presume that certain carcinomas of the kidney remain latent or grow at a very slow rate.

Wilms' tumors with a pure almost sarcomatous appearance may show cells of both epithelial and connective tissue origin. Smooth muscle and sometimes bone and cartilage may be found. Striated muscle is present in about 40 per cent of the cases. Adenomatous areas and occasional glomeruli are often also found. This complex constitution is the cause of the variegated nomenclature given this neoplasm (Figs 489 and 490).



Fig. 489

Fig. 490

Fig. 489—Sarcomatous appearance of a Wilms tumor (moderate enlargement)

Fig. 490—Adenomatous appearance of a Wilms tumor (moderate enlargement)

**METASTATIC SPREAD**—The tendency of adenocarcinomas to metastasize is directly related to their size. In a series of 149 cases reported by Bell, sixty-six of eighty-four measuring over 5 cm. showed metastases and only five of sixty-five measuring 5 cm. or less had metastasized. Adenocarcinomas spread predominantly by vessel invasion. They can reach veins either by growing toward the hilum or by piercing the capsule and contacting the veins in the perirenal tissue. Thus do adenocarcinomas spread to the lungs where they grow luxuriantly and form innumerable spherical nodules. These adenocarcinomas commonly metastasize to bones. Continuous tumor thrombi from the renal vein to the right auricle do occur. Lymph node metastases are much less frequent than in a Wilms' tumor. In Wilms' tumor metastases are commonly found within the lungs, liver, brain and regional lymph nodes; this spread is also mainly by veins. The ulcerating epidermoid carcinomas quickly metastasize to regional lymph nodes and distant metastases are almost always present when the tumor is first seen. Papillary carcinomas are slow to metastasize and only infrequently show distant spread. Death usually occurs first due to recurrence of the tumor or kidney infection.

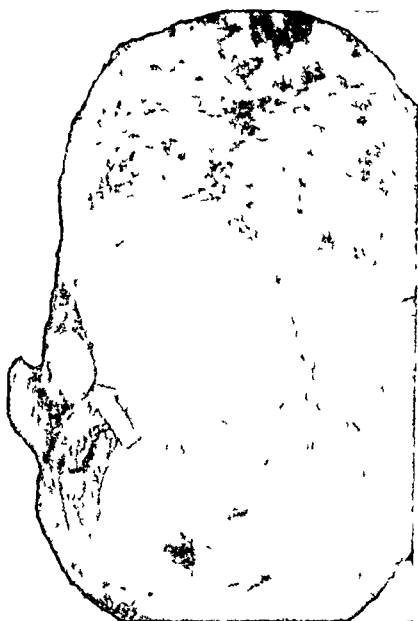


Fig. 493—Surgical specimen of the Wilms' tumor illustrated in Figs. 491 and 492. Not encapsulation with almost complete obliteration of kidney parenchyma. Arrow points to invasion of the renal vein.

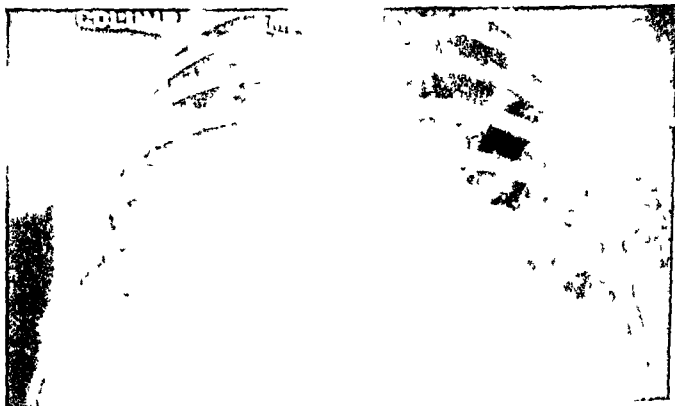


Fig. 494—Solitary metastatic mass in the right hilar region from a Wilms' tumor on 5 at follow-up operation (same patient as illustrated in Fig. 491).

for a number of years and then suddenly accelerate their growth, disseminate and cause death. The mean duration of carcinoma of the kidney in Albarran's series was 4.5 years.

*Carcinomas of the kidney pelvis* manifest themselves initially in almost all of the patients by painless but profuse bleeding. This naturally leads to a certain degree of anemia. These symptoms may be present over a relatively long period of time and hematuria may wax and wane. Often there are multiple tumors. Kimball reported that 33 per cent of seventy-four patients had tumors in the ureter and bladder as well as in the kidney at the time they were first seen by a urologist. If infection occurs there may be some costovertebral pain and fever. The immediate cause of death is often kidney infection.



Fig. 492.—Intravenous pyelogram of the same child illustrated in Fig. 491, showing a homogeneous area of density occupying the entire right side of the abdomen but with no pelvic or ureteral shadow on that side.

*Epidermoid carcinomas* often have a long preceding history of symptoms suggesting renal lithiasis. They are often accompanied by evidence of kidney infection with recurring bouts of fever, tenderness in the region of the kidney, and rather marked painless hematuria. The clinical course is quite rapid not only due to the presence of infection but also because squamous carcinomas metastasize early. Death, however, is predominantly due to kidney infection.

The *Wilms' tumor* develops insidiously and painlessly and is invariably large when first discovered (Fig. 491). Over three-fourths of the cases are found in children under 7 years of age. As the tumor grows to involve the capsule or nerves in the immediate area pain becomes apparent. In the advanced stages of the disease anorexia and weight loss appear. *Hematuria in contrast to other kidney tumors is infrequent and as a single symptom through the course of the*



Thus the kidney may be held down between the two hands and its volume, form, and consistency appreciated. Tumors developing in the upper pole of the kidney cannot usually be palpated, while those which grow on the lower pole are more accessible and consequently more easily detected. When a tumor arises in a ptotic kidney, it may be apprehended in an early stage of its evolution. On the right side, it is better detected because the liver forms a natural barrier to its growth. On the left, a kidney tumor may enlarge upward without interference from other organs.

On percussion of kidney tumors dullness is found as a rule, but a tympanic column may be found crossing the tumor area. This only indicates that the tumor is retroperitoneal; a tympanic column may also be found on percussion of many other tumors (Albarrán).

An *adenocarcinoma* of the kidney may be so small that it cannot be palpated, but if the kidney is enlarged it can usually be outlined by bimanual palpation. It does not move on respiration. The first sign of an adenocarcinoma may be bone or soft tissue metastases. Voluminous and easily palpable metastatic bone lesions may pulsate due to abundant vascularization. These bone and soft tissue metastases are often confused with primary osteogenic or soft tissue sarcomas. They usually occur in the region of the nutrient arteries, particularly of the femur. They are most difficult to diagnose when the primary tumor is occult and hematuria is absent. Biopsy usually suggests carcinoma of the kidney, and retrograde pyelography may then reveal kidney alterations.

A varicocele sometimes accompanies the kidney tumor, most frequently on the left side (Albarrán), and may be complicated by a hydrocele. On the left insertion of the spermatic vein into the renal vein takes place 2 to 4 cm. from the kidney hilum, while on the right the distance is between 2 and 3 centimeters. A primary tumor or large metastatic lymph nodes therefore have to attain a fair size before occlusion of the vein can occur. Infrequently the varicocele is caused by a simple thrombosis of the spermatic vein, but this is usually a sign of far-advanced disease.

Physical examination with papillomas and papillary carcinomas of the kidney pelvis is usually negative. If the kidney is palpable, it is usually due to a coexisting hydronephrosis. If infection occurs with any of these tumors costovertebral tenderness and fever may be present. In these neoplasms the cystoscopy frequently reveals blood coming from one ureteral orifice, and retrograde pyelograms demonstrate a filling defect.

In a *Wilms' tumor* the mass is usually large, the overlying skin is tense and shiny, and often there is a network of enlarged veins in which the blood flows from the abdomen toward the chest. On bimanual palpation the tumor is fairly firm and has an irregular surface, variable consistency and great depth. It may pulsate. If the Wilms' tumor arises on the right side and is attached to the liver, a false impression of its true size may result because of lack of definition. It may displace the transverse and ascending colon so that the large bowel extends in a diagonal line from the cecum to the anchored splenic flexure. This displacement of the bowel may be suspected because of resonance which can be outlined by percussion. If the Wilms' tumor arises on the left it may extend

disease, it is practically never found. Table XXXI, from Albarran, lists the first symptoms or signs of a Wilms' tumor. In spite of the fact that lung metastases are often massive, dyspnea is seldom present. The symptoms and signs of brain metastases appear only as a terminal event.

TABLE XXXI SYMPTOMS IN WILMS TUMOR OF KIDNEY  
(From Albarran J and Imbert, L. Les tumeurs du rein, Paris 1903, Masson & Cie.)

	CASES STUDIED	SYMPTOMS AND SIGNS		
		TUMOR (%)	PAIN (%)	HEMATURIA (%)
First symptom	98	71	20	5
During entire illness	140	96	18	16
With two symptoms	140	80		—

### Diagnosis

*Hematuria* is frequently present in kidney tumors but its presence does not necessarily indicate invasion of the kidney pelvis. Naturally the tumors which arise within the pelvis bleed much more readily than those arising from the cortical area, but hematuria may be caused simply by congestion or invasion of vessels contiguous with the tumor. There may be a considerable variation in the amount of bleeding. Hematuria is very infrequent in the Wilms' tumor, is found more often in carcinoma of the kidney and papillary carcinomas of the pelvis but is very frequent with papillomas. The epidermoid carcinoma, because of hornification and relative avascularity, does not have such marked tendency to bleed. The epidermoid carcinomas are often not diagnosed because of the long history of infection and kidney stones and their diagnosis is only made at post mortem examination.

Hematuria may occur at any time during the illness, at times there is a hemorrhage every few days. The bleeding may be regular with variation only in intensity, or it may disappear abruptly, only to reappear with the same suddenness. This uncertain characteristic is striking when the urine specimens are kept separately, for although the color of the urine remains uniform through each micturition, it may vary from bright red to normal. This variation is one of the commonest signs of renal neoplasm. If clots found in urine measure 20 cm or more in length, there is little doubt that they originated from the kidney.

*Pain and costovertebral tenderness* occur when a blood clot passing down the ureter causes contraction or when the pelvis is considerably distended by a clot. The pain can radiate either to the groin or toward the chest and if it is severe and colicky, it may suggest kidney stone.

**Clinical Examination**—Palpation of the kidneys is not always possible even in normal individuals and when a tumor is present only a careful bimanual palpation may succeed in revealing its presence. Palpation of the kidney requires that the patient be lying in dorsal decubitus and relaxed and that the examiner stand on the side of the kidney which is palpated. With one hand placed in the angle formed by the last rib and the sacrolumbar muscles, the other hand depresses deeply the anterior abdominal wall just below the costal margin.

pyelographic image (García Capurro) In *pyelitis*, clots may form within the pelvis of the kidney and further distort the renal pelvis, so that repeated pyelograms may be necessary to rule out a primary tumor of the kidney (Fig 496) On the right side, *carcinoma of the cecum and ascending colon* may simulate a kidney tumor, but carcinoma of the cecum or colon is movable from side to side Carcinoma of the kidney, in contrast to large bowel neoplasms, often may be felt deep in the flank A lesion of the large bowel usually presents occult or gross blood in the stool with changes in bowel habits Barium enema invariably reveals a characteristic bowel defect, and pyelograms are also helpful *Splenomegaly*, caused by any one of a multitude of conditions, may have to be differentiated from a kidney tumor This differentiation usually offers no difficulty because the spleen moves on respiration, is superficial, and may have a definite

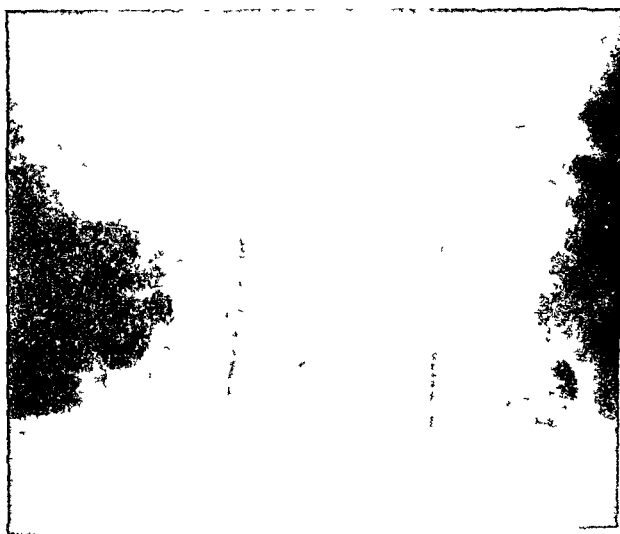


Fig 495—Retrograde pyelogram of a single cyst in the left kidney demonstrating the typical claw-hammer defect

notch Moreover there are generally other associated clinical findings *Metastatic tumors of the spleen* are rare Warren found 46 instances of metastases to the spleen in 1,140 necropsies for cancer These metastatic neoplasms are not clinically significant, for the spleen is only involved as a part of a disseminated process and does not reach a large size Cancer of the breast and malignant melanoma are the most frequent sources of splenic metastases (Fig 497), but other undifferentiated tumors can also metastasize to it *Primary tumors of the spleen*, benign or malignant, are rare (Klumbhaar) They can arise from lymph vessels, blood vessels, connective tissue, smooth muscle, or embryonic inclusions of lymphoid tissue Lymphangiomas are very rare Hemangiomas can occur (Pines), and hemangioendotheliomas, which are malignant tumors of blood vessel origin, can cause extreme enlargement of the spleen

upward and displace the diaphragm. There may also be an area of sonicity on the left between the tumor and the liver. Ascites is infrequent.

**Roentgenologic Examination**—Roentgenographic examination contributes a great deal to the diagnosis of kidney neoplasms. Roentgenograms of the abdomen may reveal a nonfunctioning kidney and show a tumor mass rarely associated with calcification. Kidney stones are rarely associated with tumor except epidermoid carcinoma of the renal pelvis. Intravenous pyelography may give leading information but a diagnosis can be seldom made with certainty on it alone. Beer felt that the failure of the kidney to excrete the dye might be due to renal vein tumor thrombosis or to compression of the venous system by tumor. In sixteen cases of adenocarcinoma with renal vein involvement, eight failed to excrete the dye and in twenty-two with no vein involvement only two failed to be visualized (Beer). Pyelography however may show a nonfunctioning kidney and may indicate irregularities of the pelvis. The best diagnostic procedure is cystoscopy combined with retrograde pyelography. With cystoscopy, a bleeding ureteral orifice can be identified and catheterized and clearly defined roentgenograms of the involved kidney can be taken. Retrograde pyelography is about 90 per cent successful in demonstrating adenocarcinoma of the kidney. In Wilms tumor intravenous pyelography may show distortion of the renal pelvis, which will not necessarily be diagnostic (Fig 492). Cystoscopy and retrograde pyelography are more accurate but are difficult in children.

With renal pelvic tumors, the defective area is irregular, constant, and extends to the margin of the pelvis, in the presence of such defect, the diagnosis of tumor of the kidney pelvis can be made provided there is no evidence of chronic infection or stone. Kidney stones have a smooth outline and the great majority of them (85 per cent) are radiopaque.

**Biopsy**—Biopsy of kidney tumors usually cannot be done before operation. Aspiration biopsy has been done in very large Wilms' tumors and at times in the soft tissue extensions of an adenocarcinoma or its metastasis. Papanicolaou (1946) has applied a technique to identify tumor cells in centrifuged urine. He believes that the identification of cancer cells in urinary sediments is easier than in vaginal or cervical smears. This procedure should be of real value in the diagnosis of carcinomas of the kidney. With an assured diagnosis the surgeon can plan his surgery more definitely before embarking upon exploration. If the urinary sediment does not show carcinomatous cells this does not, of course, contraindicate exploration.

**Differential Diagnosis**—There are several lesions of the kidney which, because of hematuria and pyelographic alterations may suggest adenocarcinoma. A single renal cyst is one of the most difficult differentiating lesions. It presents usually a well defined homogeneous pyelographic shadow in the lower pole (Fig 495). If calcification is present it is usually in the wall and curvilinear in shape. Somewhat similar changes may be observed in early carcinoma. However, carcinoma may be located in any part of the kidney, may show spotty areas of calcification within its substance, and is usually not homogeneous in density. In some instances the diagnosis can only be resolved by exploration (Wharton). Hydatid cysts of the kidney often give a typical

of the spleen occurs first in lymphosarcomas. In both lymphosarcomas and hemangioendotheliomas a generalization of the disease is frequent. The roentgenologic examination is of value in the differentiation of all large splenic tumors revealing at times calcification within the tumor, displacement of the diaphragm, displacement of the left kidney, encroachment in the greater curvature of the stomach and obliteration of the psoas muscle (Fowler). A splenectomy is the only treatment of benign and malignant tumors of the spleen, with the exception of lymphosarcoma which should be treated by radiotherapy. Unfortunately when the diagnosis of sarcoma is made the disease is invariably generalized. If a neoplasm arises in the tail of the pancreas particularly a cyst pyelography is negative and the gastrointestinal studies may reveal an extrinsic mass. *Adrenal tumors, retroperitoneal sarcomas, abdominal aneurysms and hydrops of the gall bladder* at times are confused with primary tumors of the kidney.

It is impossible to differentiate *renal tuberculosis* from a primary carcinoma of the kidney when the bladder is normal; there are no symptoms of tuberculosis of the lungs; the kidney is slightly enlarged and there is hematuria. The co-existence of tuberculosis and carcinoma of the kidney is rare. *Kidney stones* can be more easily differentiated for pain is often increased by urination or activity and is relieved by repose. The pain in kidney tumor is not influenced by urination, rest or movement. The kidney with stone is also sensitive to pressure and the urine is frequently infected. *Renal lithiasis, tuberculosis, and pyelitis* have to be differentiated from carcinomas of the pelvis.

*Primary tumors of the ureter* are extremely rare. Lazarus was able to collect only 183 cases and they occurred in the male in a ratio of 2 to 1 with the highest frequency in the sixth and seventh decades. These rare tumors can arise either from the lining mucosal epithelium or from the wall of the ureter. By far the greatest number arise from the epithelium and can be classified as papillary or nonpapillary carcinomas. These tumors are comparable to those arising from the renal pelvis. The true epidermoid carcinomas, few in number, are often associated with calculi. These tumors in their growth naturally cause obstruction of the ureter with secondary hydronephrosis and at times pyelonephritis. Metastases to regional and peritoneal lymph nodes occurred in 29 per cent of a large group collected by Lazarus. Distant metastases to liver and lungs also occurred. The first symptom of carcinoma of the ureter is hematuria. It is usually profuse, intermittent and painless but cohes is frequently present due to the formation of blood clots. This bleeding naturally causes anemia. Hematuria occurred as the outstanding symptom in 70 per cent of the reported cases (Lazarus). With ureteral block renal infection is also common and thus causes symptoms of pyelonephritis from which death usually occurs. In carcinoma of the ureter there is invariably a clear-cut filling defect in the uroterogram (Crance). By cystoscopy the tumor may be sometimes seen protruding from the ureteral meatus. Obstruction is usually encountered at the site of tumor and manipulation of the catheter produces bleeding.

A *neuroblastoma* of the suprarenal gland may have to be differentiated from the much rarer Wilms' tumor but it seldom attains a large size, and

The lymphosarcoma is the most common primary malignant tumor of the spleen and often grows to a large size. Dermoids, epithelial cysts, and mesothelial inclusion cysts have also been reported. Epidermal cysts are often quite large.



Fig. 496.—1. Pyelogram showing filling defect of the right kidney which was thought to be due to carcinoma. 2. Pyelogram of the same patient showing complete clearing of the defect forty-eight hours later. The primary cause was pyelitis plus a blood clot.

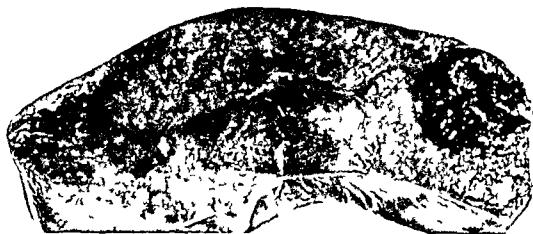


Fig. 497.—Gross specimen of a spleen revealing a well delineated black metastatic nodule from a malignant melanoma.

(Bostick) and occur in young individuals (Shawar). Primary tumors of the spleen usually develop without symptoms until a mass and later a dragging sensation are noticed. Infarction with sudden pain may occur in both benign and malignant tumors. Lymph node involvement in the region of the hilum

**SURGERY**—A kidney tumor can be cured best by radical surgery. The size of the tumor is not necessarily a contraindication to its removal. The lumbar approach is satisfactory for the excision of small kidney tumors. However, in Wilms' tumors, the abdominal approach is favored by Ladd, because this facilitates the ligation of the renal pedicle as a preliminary step to the surgical removal. A second important advantage of the abdominal approach has been stressed by Sugarbaker: the possibility of removing the tumor within the anatomic envelope of the kidney. The posterolateral approach requires the entering of Gerota's fascia in order to reach the hilar structures, such a procedure is often followed by recurrence. At the time of operation, tumor may be found growing into the renal vein, necessitating partial resection or even ligation of the vena cava (Pfaff). In other instances the findings at exploration (distant lymph node metastases, liver metastases) may contraindicate the completion of the surgical procedure.

Rarely an adenocarcinoma of the kidney may produce a single metastatic nodule in the lung. Barney reported on a patient who had a nephrectomy followed by lobectomy for a single pulmonary metastasis in July, 1933, who was free from evidence of recurrence in January, 1945.

For papillomas and papillary carcinomas of the pelvis, the entire kidney and the ureter, including the intramural portion within the bladder wall, must be removed, even if the ureter is not grossly involved by tumor. This radical operation is necessary because of the high percentage of local recurrences in the remaining portion of the ureter. Ulcerative carcinomas of the kidney pelvis are seldom operable but should be treated by nephrectomy. The treatment of carcinoma of the ureter is nephroureterectomy.

### Prognosis

*Adenocarcinoma of the Kidney*—The smaller the tumor, the less chance of distant metastases, therefore, the best prognosis may be given to those in whom the tumors are diagnosed early. The patients with a doubtful diagnosis or in whom the tumor is small at the time of operation have a good prognosis (Wharton). On the other hand, large tumors may be present for many years without metastasizing and small tumors may show wide dissemination. Mintz emphasizes that 15 to 50 per cent of the patients surviving for five years develop recurrences after that period. Between 1900 and 1923 Mintz operated on sixty-two patients, seven lived over five years, but of these, three had recurrences in the next five years, leaving only four actual survivals. Between 1924 and 1935 he operated on 65 patients, ten lived over five years, but five of these had recurrences in the next five years, leaving only five patients surviving ten years. In other words, 9 of 127 patients (or 7 per cent) lived ten years. This report disregards patients who refused operation or were inoperable when first seen. In Priestley's series there were 395 patients operated on, 187 lived three or more years (47 per cent) and 137 lived five or more years (35 per cent). This series did not include inoperable cases. There were approximately 15 per cent five-year survivals in 100 consecutive cases.

before it becomes palpable it has usually metastasized to bone, liver, lungs or regional lymph nodes. Wilms' tumors rarely metastasize to bone while neuroblastomas have bone metastases in a large percentage of cases. Retroperitoneal lymphosarcoma, if present, is usually accompanied by peripheral lymphadenopathy. A splenomegaly, which, in a child, is usually due to some blood dyscrasia, must be differentiated from Wilms' tumor. The enlarged spleen moves on respiration, hematologic findings and pyelograms will also usually serve to distinguish. A massive hydronephrosis may be easily confused with a Wilms tumor because of its size or failure of the kidney to be visualized by pyelograms. It will not diminish in size under radiotherapy and the diagnosis may be made only at exploration. Ovarian tumors, omental cysts, and new growths of the liver have all been confused with Wilms' tumor, but these conditions are extremely rare and usually have other identifiable characteristics which are sufficient for differentiation.

### Treatment

ROENTGENTHERAPY — Adenocarcinomas of the kidney are at times rather radiosensitive but their treatment by means of radiations is not justified if surgical intervention is possible. Radiotherapy may serve as a very good means of palliation in the inoperable or recurrent group of cases. Carcinomas of the kidney pelvis are theoretically radiocurable, but the problem in the treatment of these tumors is further complicated by the frequent existence of other carcinomas in neighboring areas of the ureter. Their radical surgical removal has proved successful and no pathologically proved case has been reported controlled by means of radiations.

Wilms tumors are notably radiosensitive. Roentgentherapy of these tumors contributes a rapid clinical improvement with marked or complete regression but most patients thus treated later die because of development of pulmonary metastases. Whether radiotherapy applied to early cases could be successful in itself to control a worthwhile proportion of these tumors is an academic question. Preoperative roentgentherapy has been advocated to reduce the operative mortality which, in general, attends the removal of these voluminous tumors. Ladd, however, has removed twenty-two Wilms' tumors without operative mortality and without benefit of preoperative roentgentherapy (Scholl). Whether preoperative roentgentherapy improves the final results has never been proved, it is argued that it may increase the late mortality, for metastases could develop in this interval before performing the radical removal. Some authors advocate the administration of postoperative roentgentherapy on the basis of the fact that this procedure has resulted in permanent control of cases when it was known at operation that portions of tumor had not been removed (Sugarbaker, Nesbit). Nesbit reported on a patient with pathologically proved inoperable Wilms' tumor, treated by roentgentherapy alone, who has survived over ten years.

In the treatment of inoperable kidney tumors of all varieties, roentgentherapy contributes a marked palliation in most cases. Roentgentherapy is also of palliative value in the treatment of metastases.



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The presence of vein invasion is a very important factor in the prognosis of patients with adenocarcinomas of the kidney. Of 207 who had renal vein involvement, sixty (29 per cent) were alive after five years in the remaining 186 without vein or lymphatic involvement, 103 (55 per cent) were alive after five years (McDonald).

*Papillary and Epidermoid Carcinomas of the Kidney Pelvis*—The prognosis of tumors of the kidney pelvis is conditioned largely by the type of operation done. In the group reported by Kimball, forty patients were treated by nephrectomy; there were thirty recurrences, twenty one second recurrences, and an operative mortality rate of 33 per cent. Eighty six per cent of all the recurrences appeared in the ureteral stump. There is no informative large series of cases with nephroureterectomy, including the removal of the intramural portion of the ureter. This operation should materially reduce the number of local recurrences. The prognosis of the epidermoid carcinoma of the kidney pelvis is invariably very poor.

*Wilms' Tumor*—The age of the patient, the size of the tumor, and the pathologic character do not influence the prognosis. A Wilms' tumor may be considered cured in 95 per cent of the cases if eighteen months have elapsed after operation without evidence of local recurrence or distant metastases (Priestley), because about 90 per cent of these appear in the first year (Fig 494). The overall prognosis of Wilms' tumors is certainly better than is generally appreciated. The best results have been reported by Ladd of fifty six patients operated on, fourteen (25 per cent) remained well from two to twenty one years after operation (Scholl). Hematuria is usually an ominous sign. None of ten patients with hematuria reported on by Ladd survived. Table XXXII is an estimate of the approximate five year survival figures which can be obtained by using the most modern methods of diagnosis and treatment.

TABLE XXXII APPROXIMATE LIFE EXPECTANCY OF PATIENTS WITH KIDNEY TUMORS AFTER ADEQUATE SURGICAL TREATMENT

TYPE OF TUMOR	FIVE YEAR SURVIVALS (%)
Ulcerative squamous carcinoma	0
Wilms' tumor	10-15
Adenocarcinoma of kidney	15-25
Papillary carcinoma	25-35
Papilloma	35

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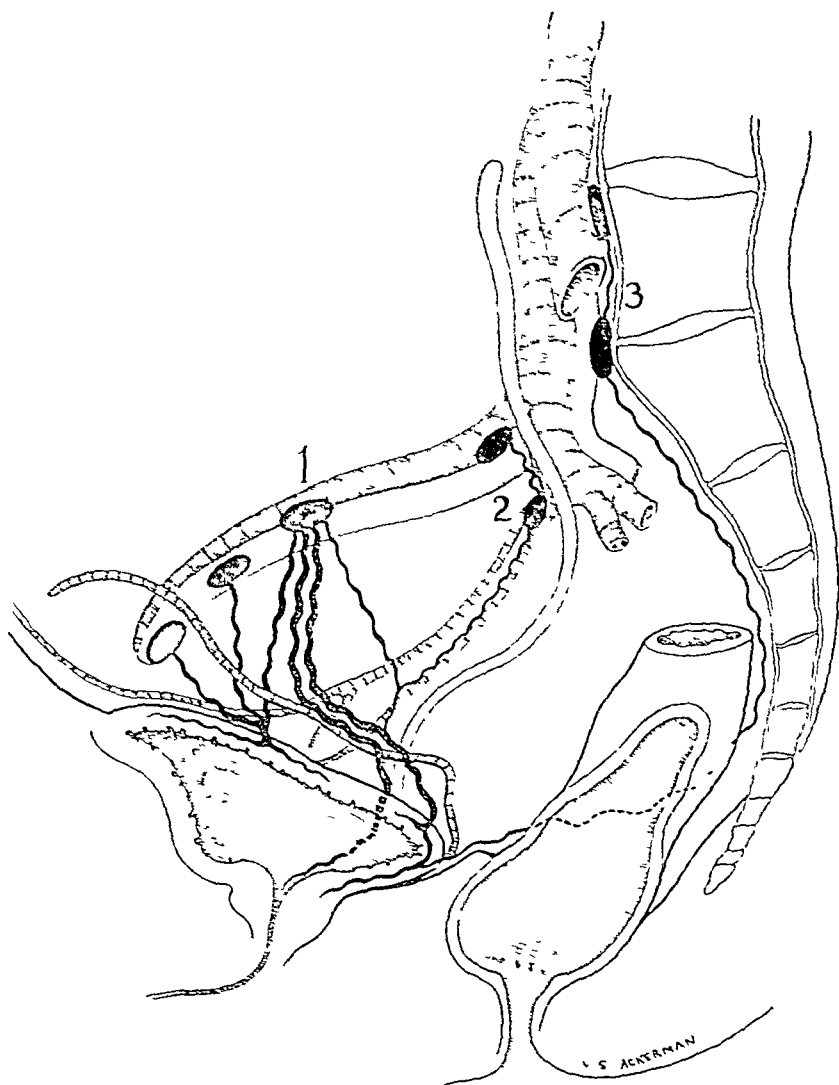


Fig 495.—Anatomic sketch of the lymphatics of the bladder drained mainly by, 1 the external iliac nodes but also by 2, hypogastric and, 3 common iliac nodes

## CARCINOMA OF THE URINARY BLADDER

## Anatomy

The urinary bladder is a muscular membranous sac occupying the anterior part of the pelvis and the lower abdomen. It has the form of a tetrahedron with a posteroinferior triangular base, the trigone, extending from the origin of the urethra to the ureteral orifices. Its posterosuperior wall extends from the urachus to the ureteral orifices, and the anterolateral walls join it to complete the tetrahedron and end in an anterosuperior summit at the point of fixation of the urachus.

The inferolateral surfaces are related to the endopelvic fascia covering the levator ani muscles and extend upward to the level of the arcus tendineus. With distention the obturator nerve and vessels, umbilical artery, and ductus deferens are brought into relationship with this surface. The fundus, with a more fixed position, is directly related to the seminal vesicles in the male, portions of the vas deferens, and the ampullary portion of the rectum. In the female it is related to the anterior surface of the vaginal wall and corpus uteri. In the male the inferior angle of the bladder at the urethral orifice rests directly on the base of the prostate from which it gains support through the puboprostatic ligaments of the endopelvic fascia. In the female this point is attached to the transverse sphincter urethra muscle with a similar fascial support. The superior angle continues onto the anterior abdominal wall as the median umbilical ligament. The arterial supply to the bladder is derived from the superior and inferior vesical branches of the hypogastric artery. The venous drainage forms a plexus in the lower fundic area which empties into the hypogastric veins.

**Lymphatics**—The mucosa and the muscular layers of the bladder possess rich intercommunicating networks of lymphatics (Albarran). According to Rouviere they give rise to the following collecting trunks:

*Collecting Trunks of the Trigone*—These trunks emerge from points in the bladder medial to the ureters or to the deferent ducts. They follow the uterine or the deferent artery and terminate in the medial and middle groups of nodes of the external iliac chain. Frequently there is an intercalating nodule in the pathway of these trunks.

*Collecting Trunks of the Posterior Wall*—The lymphatics arising from these trunks may follow different directions: (1) they may reach the posterolateral angle of the bladder, cross the umbilical artery, and terminate in one of the nodes of the medial and middle group of the external iliac chain, (2) less frequently they may terminate in the retrofemoral lymph nodes, (3) they may empty into one of the collecting trunks of the trigone, (4) they may terminate in the hypogastric lymph nodes or in a lateral lymph node of the external iliac chain.

*Collecting Trunks of the Anterior Wall*—These trunks converge toward the middle third of the lateral border of the bladder in the region of the middle vesical artery. They descend toward the origin of the middle vesical and umbilical arteries, meet the collecting trunks of the posterior wall, and merge with them, ending in the nodes of the external iliac chain.

with it makes its appearance at an early age (between 30 and 40 years). It is estimated that from 70 to 90 per cent of the population of Egypt is infected with *Schistosoma haematobium* (bilharziasis).

### Pathology

**Gross Pathology**—*Papillomas* are definitely premalignant tumors and some pathologists even designate them as Grade I carcinomas. The difference in evaluation must, of necessity, also influence the reports of end results. These papillomas, in undergoing transition to carcinoma, become carcinoma of the transitional-cell type.



Fig. 499—Surgical specimen of bladder showing extensive papillomatosis.

The papilloma arises on the paler mucous membrane of the bladder and has a large base which hides the point of implantation like a mushroom hides its base. It is pink or red in color, it is friable and soft. Only under some tension does it become evident that the papilloma is attached by an often flat and very soft pedicle formed, for the most part, by the mucous membrane itself. At times the bladder can be entirely replaced by papillomas (Fig. 499). If multiple papillomas are present, some may be benign and others malignant, but there is no correlation between the gross appearance of a papilloma and its benign or malignant character. After a papilloma has become definitely malignant, it tends to invade the base and become fixed. Later, it ulcerates and becomes infected.

In summary, the lymphatics of the bladder are drained particularly by the medial and middle groups of nodes of the external iliac chain but occasionally also by the hypogastric and the common iliac nodes (Fig 498)

### **Incidence and Etiology**

Of 902 epithelial tumors of the bladder collected by the Carcinoma Registry of the American Urological Association 76 per cent were in males and 24 per cent were in females (or a ratio of 3 to 1) The age incidence showed that 62 per cent occurred in patients between 50 and 69 years of age

Carcinoma of the bladder may occur as an occupational disease in workers of the dye industry The number of these industrial bladder tumors has increased in proportion to the development of the coal tar dye industry They were first described in Germany (Rehn) but have since been reported in Switzerland, England, Wales, Russia, Italy, and the United States All of the approximately 600 reported cases were in males The number of cases from any one plant naturally varies according to the type of chemical used and produced, the manufacturing process employed, and the precautionary measures taken

Of the 902 bladder tumors collected by the Carcinoma Registry, only 16 occurred in aniline dye workers The dye most commonly blamed for causing occupational bladder carcinoma is aniline This accusation, however, is incorrect, for there are many related compounds which can initiate tumors of the bladder The commonest substances are the products of coal distillation, namely, tar and its derivatives (aromatic amino and nitrocompounds, coal tar dyes paraffin, etc) Oppenheimer (1927) reported that the period of exposure to the dyes ranged from one to forty one years This long latent period between exposure and development of tumor might readily explain why some cases are not diagnosed as occupational Hueper produced pathologic lesions in the bladders of fourteen of sixteen dogs which were exposed over a long period of time to commercial betanaphthylamine He showed that this carcinogenic agent is powerful enough to overcome any degree of individual constitutional resistance and that the duration and intensity of exposure are more important than a pathologic tissue scintity or inherited neoplastic predisposition

There is a definite association between leucoplakia and epidermoid carcinoma of the urinary tract Leucoplakia results from metaplasia of the transitional epithelium of the bladder It can exist independently and can precede or accompany an epidermoid carcinoma The metaplasia is initiated by long-standing chronic inflammation or mechanical irritation plus unknown factors In 124 cases of leucoplakia of the urinary bladder collected by Rabson, eighteen were associated with carcinoma (13 epidermoid) and one with sarcoma Patch found thirteen cases of leucoplakia of the bladder, seven coexistent with epidermoid carcinoma in the bladder and one with simultaneous epidermoid carcinoma of the bladder and left kidney pelvis

Cancer of the bladder may develop in patients with bilharziasis, a parasitic infection which is definitely a predisposing factor in cancer of the bladder (Ferguson) This disease occurs almost always in men, and cancer associated

but the majority of transitional-cell carcinomas develop as a papillary mass *Epidermoid carcinomas* (only a small percentage of the total number of carcinomas) are usually firm, deeply ulcerated, and heavily infected and often involve the musculature of the bladder (Fig 500)

In 473 single bladder tumors collected by the Carcinoma Registry of the American Urological Society, the points of origin were outlined as follows

REGION	NUMBLP	PERCENTAGE
Trigone	130	27
Lateral walls	199	42
Bladder neck	28	6
Posterior wall	52	11
Vault	36	8
Anterior wall	28	6
	<hr/> 473	<hr/> 100

In 243 cases reported by Barringer, 195 (80 per cent) were around the bladder base near or involving the internal urethra or one or both ureters. In another series reported by the Registry, there were 643 single and 250 multiple bladder carcinomas, 45 per cent of which were larger than 5 centimeters.

Carcinoma of the bladder gradually extends through the wall, the speed of its extension being related to the degree of differentiation. It seldom invades the prostate, contrary to the very frequent spread to the bladder by carcinoma of the prostate. Invasion of the seminal vesicles, urethra, and ureters is rare. In unusual instances the large bowel may be invaded.

**METASTATIC SPREAD**—It is often maintained that carcinoma of the bladder tends to remain localized. There is no doubt that in autopsies of patients who have died with marked infection and concomitant pyelonephritis, or in patients dying of complications after surgical removal of an early lesion, there may not have been time for metastases to develop. However, Albarrán (1891) found lymph node metastases in eleven of seventeen post-mortem examinations. Metastatic disease was found most frequently at the bifurcation of the iliac artery, but in a few cases the lymph node involvement extended up to the level of the diaphragm. Saphin believes that if a primary carcinoma of the bladder has invaded the prostate in the male or the parametria in the female, the chance of there being metastases is materially increased. Colston and Leadbetter found metastatic disease in 61 per cent of 98 cases of infiltrating tumors of the bladder which came to autopsy. Involvement of the retroperitoneal lymph nodes, liver, lungs, and bone was frequent. Spooner reported 167 autopsies of carcinoma of the bladder, many of which were done on patients who had died in relatively early stages of the disease because of infection or other postoperative complications. Metastases were found in forty-nine patients (29 per cent). The lymph nodes were involved in thirty-four, one or more distant viscera contained disease in twenty-four, and the liver was involved in fourteen. Spooner expressed doubt as to the thoroughness of the search for metastatic disease at necropsy in the average case of carcinoma of the bladder. He advised a careful search through the adipose and areolar tissue of the iliac and hypogastric grooves. Jewett studied a group of patients with carcinoma of the blad-



Fig .00 —Surgical specimen of an epidermoid carcinoma of the bladder



Fig .01 —Post mortem specimen of papillary carcinoma of the bladder. Death resulted from urinary infection.



a carcinoma is far advanced and quite undifferentiated, it may be difficult to tell whether it originated in the prostate or the bladder. The epidermoid carcinomas are often fairly undifferentiated and heavily infected (Fig 502)

### Clinical Evolution

*Hematuria* is the most common presenting symptom. In 163 patients reported on by Smith, 125 had hematuria. Hematuria often appears abruptly without pain and is not relieved by repose or motion. Its persistence and repetition are the most important characteristics of the evolution of the disease. There is often disproportion between the amount of bleeding and the amount of disease present. One micturition may be bloody while the next is entirely clear, or the urine may change slowly to a normal color over a period of days. In some instances the amount of bleeding may be very marked, and if clots appear, they may be followed by enormous enlargement of the bladder and by painful spasms of the bladder musculature. With removal of the clots, the pain ceases. Hematuria is often most prominent in the terminal stages of a carcinoma of the bladder (Albarrán) but may be very severe, even with benign papillomas. Table XXXIII indicates the frequency of symptoms and those which are most common initially.

TABLE XXXIII TABULATION OF INITIAL SYMPTOM AND LATER SYMPTOMS AND THEIR INCIDENCE IN 902 CASES OF CARCINOMA OF THE BLADDER  
(Committee of the Carcinoma Registry, American Urological Society)

	NUMBER OF CASES
Initial Symptom	
Hematuria	573
Frequency of urination (pollakiuria)	176
Dysuria (painful micturition)	40
Pain unrelated to urination	16
Difficulty in urination	16
Acute retention	7
Total	828
Symptom	
Intermittent hematuria	704
Constant hematuria	122
Frequency of urination (pollakiuria)	614
Dysuria (painful micturition)	375
Pain unrelated to micturition	312
Retention of urine	113
Urinary incontinence	19
Passage of fragments of tumor	32

The removal of benign papillomas does not necessarily mean cure, for they are likely to recur in a few years. Then again the evolution may last ten to twenty years with intermittent hematuria, at which time and for no apparent reason the tumor takes on an aggressive character and becomes malignant. The hematuria in this case tends to become more brisk and constant, and if the tumor is not treated rigorously and appropriately, death may follow. If the tumor is malignant from the start with symptoms present for only a few months, treatment must be immediately instituted because swift invasion of the bladder and neighboring organs and metastases to nodes and distant organs occur.

der and found that in three, who had submucosal infiltration only, no metastases were present. In fifteen with infiltration to the muscle, only one presented metastases. In eighty-nine in whom the tumor had extended to the perivesical tissue, metastases were present in fifty-two. Of these fifty-two with metastases, the regional lymph nodes were involved in thirty-three, the liver in twenty-six, the lungs in eighteen, and the bones in eleven. In 36 per cent of all the patients with metastases, no regional lymph node involvement was found.



Fig. 50.—Photomicrograph of an epidermoid carcinoma of the bladder (moderate enlargement).

**Microscopic Pathology**—Tumors of the bladder arise, for the most part from the transitional epithelium, and when they form papillomas they are supported by an abundantly vascularized connective tissue stroma. The connective tissue in a *benign papilloma* is in the center and forms the framework for lobules. When the tumor becomes malignant, it invades these lobules and connective tissue is often seen about the periphery. Some of these tumors may contain nerves and small collections of smooth muscle cells. The location of the recurrent papillomas or early transitional carcinomas corresponds exactly to the opposing points of the mucosa. *Malignant changes* in a papilloma are found not only in the base, but frequently in the peripheral portions accessible to biopsy. These changes may be localized so that one area of a papilloma may be benign while another portion is malignant. With the frankly ulcerating *transitional-cell carcinoma*, the origin from transitional epithelium is still apparent. As the tumor becomes more undifferentiated, it shows a tendency to infiltrate diffusely, and destruction and permeation of the bladder musculature by masses of tumor cells within the lymphatics are seen quite frequently. When

defined, pedunculated tumors, particularly multiple tumors, are usually benign, but if the tumor has a broad infiltrating base, it is generally malignant (Pfahler). Pneumocystograms usually show the degree of infiltration of ulcerated tumors.

**Differential Diagnosis**—Because a very high percentage of carcinomas of the bladder produce hematuria, other lesions presenting this symptom have to be ruled out. In 860 patients with hematuria, it was caused by lesions of the kidney in 331 and by lesions of the bladder in 307. Of these 307 patients, the hematuria was caused by tumor in 235 (163 carcinomas and seventy-two papillomas). The other causes were lithiasis (thirty-one cases), tuberculosis (fourteen cases), and cystitis (six cases). There were 126 lesions of the prostate and fifty-four of the ureter (Krietschmer).



Fig. 50. - Roentgenogram of the bladder showing multiple irregular filling defects with contrast due to multiple papillomatosis.

*Tuberculosis* may be mistaken for tumor. Fairly often, however, there is evidence of tuberculosis in the epididymis or seminal vesicles, or pyelograms may show a primary lesion in the kidney. Practically all cases of tuberculosis of the genitourinary tract are secondary to primary lung lesions. Biopsies may show tuberculosis, and guinea pig inoculation, if positive, is unequivocal proof of the presence of acid-fast infection. The hematuria which is present in tuberculosis is usually not as marked, frequent, or as painful as in carcinoma of the bladder.

*Carcinoma of the female urethra* is a relatively rare lesion, the average age was 53 years in the 109 patients reported on by Menville. There is no evidence that urethral caruncle predisposes to its development. Carcinoma of

## CANCER OF GENITOURINARY TRACT

Carcinoma of the bladder varies in the speed of its evolution. The tumors which begin as papillomas may undergo very gradual transition to carcinomas. The papillary type of carcinoma tends to grow more slowly than the deeply ulcerating variety. Since a high percentage of the tumors grow in close relation to the ureters, urinary infection is common. It produces fever, weight loss, and costo-vertebral tenderness. The patient with untreated carcinoma of the bladder usually dies of urinary infection associated with unilateral or bilateral pyelonephritis. It is most uncommon for extensive generalized metastases to be the cause of death (Fig 501).

### Diagnosis

**Clinical Examination**—A tumor of the bladder can be best felt by rectal or vaginal palpation further supported by pressure on the hypogastrium and with the patient under spinal anesthesia. At times the tumor can be felt supra pubically. The bladder should, of course, be empty. Perivesical extension may be detected by this palpation. This examination may be unsatisfactory if the prostate is enlarged.

**Cystoscopy**—Cystoscopic examination of all bladder tumors is essential. The typical papilloma is attached by a delicate pedicle usually to the lower lateral or posterior bladder wall. Its grayish pink branches float in the irrigating fluid, giving the appearance of sea weed (Lowsley). With infection the tips of this fernlike growth become edematous and necrotic. It is not always possible on cystoscopy to differentiate the benign from the malignant papilloma. In early papillary carcinoma the base is infiltrated. In the deeply ulcerating tumors the surrounding mucosa is often thrown up into folds. With carcinomas secondary infection may be present which also contributes to the rigidity of the wall. The capacity of the bladder is often reduced. It may be difficult to differentiate the appearance of this type of carcinoma from tuberculosis, chronic inflammatory lesions, and particularly, encrusted phosphatic cystitis.

**Biopsy**—Biopsy through a cystoscope may be difficult because of the secondary infection present. A negative biopsy in the presence of an apparent carcinoma should always be repeated. We have found it of value to wash out the bladder, filter the fluid, and make paraffin sections of the embedded sediment.

**Roentgenologic Examination**—Scout films of the abdomen may reveal large soft tissue masses in the region of the bladder, particularly before treatment, for every case of carcinoma of the bladder. Pyelograms are indicated in order to appraise the presence or absence of kidney damage. Cystography with the use of opaque substances injected into the bladder may be helpful. Lowsley at the Brady Foundation uses diastat and umbrathor as contrast media, for he feels that umbrathor gives a good relief picture of irregularities in bladder shadows (Fig 503). Pfahler has advocated, since 1908, the injection of air in preference to the use of opaque materials. Pneumocystograms are of particular value when cystoscopy is hampered by obstruction of the ureters or hemorrhage. The normal bladder distends smoothly and evenly. Sharply

known to cause carcinoma of the bladder. Employment should be limited to a maximum of three years, and frequent routine cystoscopic examinations should be done. If at any time there is evidence of any changes in the bladder suggestive of beginning neoplasm, the workers should immediately be taken out of their occupational environment (Hueper).

**CYSTOSCOPY**—Fulguration of small papillomas through the cystoscope is often effective. Because recurrences may repeatedly appear, it is necessary that careful follow-up with cystoscopic examinations be carried out. Large papillomas must be fulgurated through suprapubic cystotomy.

**ROENTGEN THERAPY**—Because a good proportion of the tumors of the urinary bladder are transitional-cell carcinomas which are very radiosensitive and radiocurable, external irradiation might be expected to be relatively successful. However, the irradiation using equipment of 200 kv. seldom accomplishes the total sterilization of these tumors. This is in great part due to the lack of sufficient penetration, but there may be other factors involved. Roentgentherapy as a palliative measure also gives unsatisfactory results. When heavy irradiation does not sterilize the tumor, the contracted bladder and residual or recurrent disease produce lasting pain (Nesbit).

Irradiation with "supervoltage" equipment has given encouraging results (Buschke), but even when the treatments are protracted over several weeks and are administered under clinical control, tumors which have invaded the bladder musculature are not cured. External roentgentherapy has not as yet yielded a sufficient proportion of good results to justify its use in preference to other methods.

**CURIE THERAPY**—The interstitial implantation of radium finds one of its most useful indications in the treatment of these tumors. In some instances the implantation of radon seeds may be carried out through the cystoscope, but the implantation of seeds through a suprapubic cystotomy renders the procedure considerably more accurate. The exophytic part of the tumor may be removed and the radon seeds homogeneously distributed on the wide base of the tumor. If the tumor is near the ureters, ureteral catheters may be inserted (Barringer). In infiltrating tumors, the sources of radiations may be placed deeper, but in such cases the homogeneity of the irradiation is considerably less satisfactory and the radiations consequently less effective. An appreciable number of the patients treated in this manner develop severe infections of the bladder and kidneys. As a result of inadequate distribution of radiations, there may be late radionecrosis manifested in the form of suprapubic, urethrorectal, and vesicovaginal fistulas. The urethra may undergo stricture. Death occurs in about 4 per cent of the cases (Nesbit).

**SURGERY**—Local surgical resection of accessible microscopically verified papillomas may be done successfully through a cystostomy. If possible, the base of the excised specimen should include bladder musculature. Well-localized carcinomas located in the vertex or anterolateral or upper posterior wall of the bladder can be locally resected (Young).

Before radical surgical treatment of carcinoma of the bladder is undertaken, the form, size, location, and histologic features of the tumor should be known,

the urethra may be confused with carcinoma of the bladder in the female because the urethra is implicated in the development of carcinoma of the bladder. However, the tumor may be felt early as an induration along the urethra, and at times it may even project from the urethra. Inguinal lymph node metastases can occur (Clayton). These carcinomas of the urethra are usually epidermoid but can also be adenocarcinomas.

**Kidney tumors** are not difficult to differentiate, for on cystoscopy blood is often seen coming from the ureteral orifice of the involved kidney. The presence of a mass in the kidney region is confirmatory evidence.

Simple chronic interstitial cystitis may be difficult to differentiate because the induration and infection so strongly suggest bladder carcinoma. Repeated biopsies and cystoscopic examinations may be necessary to rule out tumor. Stone accompanying cystitis also produces an induration around the bladder and may cause an erroneous diagnosis of cancer. Tumor may coexist with cystitis and this may give a false impression of a tumor much larger than is really present. Lesions of the prostate may cause hematuria, but again rectal and cystoscopic examinations usually suffice to differentiate them.

Direct invasion of the bladder by tumors of other organs is quite common, particularly the prostate, cervix, and rectum. The primary source of these tumors can usually be determined by careful pelvic and rectal examination or by biopsy.

Primary carcinomas and papillomas of the bladder apex are relatively rare but they have to be distinguished from the mucinous adenocarcinoma arising from the epithelium of the urethral canal. Begg collected thirty-four cases of adenocarcinoma of the urethra showing areas of circumscribed ulceration. These lesions may, at times, be papillomatous but their location and biopsy resolve the diagnosis. Treatment consists of the excision of the umbilicus with the intervening tissues between it and the bladder and of a wide radical resection of the primary tumor (Begg).

Other rare tumors of the bladder are neurofibromas (Thompson), leiomyomas (Kretschmer), fibromyomas (Higgins), hemangiomas (Ballenger) and leiomyosarcomas. Leiomyosarcomas usually occur before the age of 12 or after 45 years. They arise from the wall of the bladder and rarely metastasize, and surgery is the treatment indicated (Kretschmer). Rhabdomyosarcomas occur almost always in infancy. According to Albarran, sarcomas are most common on the posterior wall and the anterior segment of the bladder. The prognosis is poor with surgery offering the only chance of cure (Uhlmann). Primary urethral carcinomas are exceedingly rare, highly malignant, metastasize early, and can be cured only by surgery (Keen).

### Treatment

**PREVENTION**—Prevention of occupational tumors is possible for the carcinogenic agent doubtless enters the respiratory tract and protection can and should be utilized. Workers admitted into industrial plants which use aromatic amines should be healthy, between 20 and 45 years of age, and should not have had any previous history of occupational exposure to those agents which are

TABLE XXXIV RESULTS OF INTERSTITIAL IRRADIATION OF CARCINOMA OF THE BLADDER BY RADON SEEDS, MOST CASES TREATED THROUGH SUPRAPUBIC CYSTOTOMY  
(After Barringer, B S J A M A, 1942)

TOTAL NUMBER—257	PALLIATIVE OPERATION OF NO TREATMENT	LOST FOLLOW UP OR DIED OF INTERCURRENT DISEASE	CURED OVER FIVE YEARS	PERCENTAGE
112 Papillary carcinoma	3	20	50	45
145 Infiltrating carcinoma	12	12	35	24

the bladder for whom cystectomy was done by Graves, ten were living and well, but the majority had been followed only for a short period of time

Wirth, Cantril, and Buschke treated sixty-eight patients with carcinoma of the bladder at the Tumor Clinic of the Swedish Hospital of Seattle with 800 kv external roentgentherapy. Ten of their patients were living and well without evidence of disease five years or more following treatment. It is to be expected that further study of this form of treatment will contribute better results in the future.

The prognosis of bladder tumors varies with the evolution of the disease. These tumors may be divided into three main groups: tumors always benign, those benign which become malignant, and those which are always malignant (Albarrán). The benign tumors may have an extremely long evolution with lapses of a few months to five years between episodes of hematuria.

Jewett related prognosis to the degree of extension. If the tumor is only in the submucosa or muscle, the chances of metastases are low. When tumor extends to the perivesical tissue, the chances of metastases are high. He believes that posterior wall tumors are associated with metastases much less frequently than those arising from one of the other walls because the lymphatics of the posterior wall run the longest course. The prognosis is markedly improved if the tumor is 2 cm or less in diameter, but about 45 per cent of the lesions are larger than 5 cm in diameter when first seen (Committee of the Carcinoma Registry).

Because such a high percentage of these tumors (approximately 80 per cent) are located in close proximity to the trigone, infection of the genitourinary tract is common. The presence or absence of this infection and the amount of functioning kidney tissue present are very frequently the sole determining factors of whether a patient lives or not. In some instances it is true that the infection can be controlled or stabilized so that cure of a local condition can still be effected. If, however, when the patient is first seen there has been irreparable profound kidney damage, hope of cure is impossible and death results from kidney insufficiency. Death from widespread dissemination of the disease is relatively infrequent.

The evaluation of figures on cure rates of bladder carcinomas often depends on the pathologist's interpretation of what constitutes a malignant neoplasm. If he designates all papillomas of the bladder as Grade I carcinomas and there happens to be a high percentage of these in the reported group, naturally the cure rate will be abnormally high. This factor must constantly be kept in mind when evaluating any series.

plus the amount of infiltration and the presence or absence of metastases. This information may be obtained by rectal palpation, cystoscopic examination, biopsy from the base of the growth, pyelograms, and pneumocystograms. The general condition of the patient must be thoroughly evaluated, with special emphasis placed upon the cardiovascular and renal reserve (Dean).

Nesbit has clearly outlined the indications for cystectomy in frank carcinoma and papillomas:

- 1 Cases presenting involvement of the trigone so that the ureteral orifices cannot be spared when destructive methods of treatment are used
- 2 Those presenting infiltrative involvement of the vesical outlet, so that adequate attack locally is destructive to the sphincters
- 3 Multiple infiltrative tumors
- 4 Neoplasms of low degree of malignancy which show a marked tendency to recur and spread all over the bladder in spite of conservative treatment, and eventually become penetrative or highly malignant

The success of a cystectomy depends on the effectual transplantation of the ureters. They may be transplanted into the sigmoid, the perineum, the rectum, the urethra, the vagina, into the skin near the incision, in the surgical wound, or near the anterosuperior iliac spine (Hinman). Nephrostomy and lumbar ureterostomy may be done. The nephrostomy and the skin transplantation seem to have the lowest operative mortality, but the necessity of taking care of the urine through the use of an artificial bladder makes this operation undesirable. Transplantations into the vagina and urethra have a high operative mortality. Transplantation into the rectum often causes death from kidney infection. At our hospital Sugarbaker has employed a procedure which has definite promise. In the first stage the large bowel is divided, the proximal loop forms a permanent colostomy, and the distal loop is to become an artificial bladder. The ureters are freed and anchored into the wall of the sigmoid. The lumens of the ureters are opened so that urine may pass either into the large bowel or into the bladder. In the second stage, the cystectomy is performed, the ureters are separated and at the point where they have been embedded in the bowel, the division into the lumen of the blind loop is completed. The anal sphincter remains. Urine can be retained for relatively long periods of time. The use of an uninfected blind loop of bowel for an artificial bladder should materially reduce urinary complications. Unfortunately not enough of these operations have been done to determine their practicability. The number of cases suitable for cystectomy makes up a relatively small percentage of all carcinomas of the bladder.

### Prognosis

The prognosis of a large group of patients treated by Barringer with radium implantation is shown in Table XXXIV. In 600 patients with malignant tumors of the bladder treated by various surgical procedures 165 (28 per cent) were cured for five years or more. In sixty seven of these 165 there were recurrences after five years (Counseller). The operative mortality for cystectomy is high even in the most experienced hands. Death usually results from kidney infection. In a group of twenty eight patients with malignant disease of



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passes above the terminal segment of the ureter to terminate in one of the middle nodes of the external iliac chain (Cunéo)

2 The *hypogastric pedicle* arises from the inferior aspect of the prostate, travels toward the posterior surface of the gland, and then turns outward along the prostatic artery to terminate in one of the hypogastric nodes

3 The *posterior pedicle*, composed of two or three trunks, arises from the posterior surface of the prostate and follows an anteroposterior direction toward the sacrum to end in lymph nodes located on the medial side of the second sacral foramen or in other nodes in the region of the promontory of the sacrum



Fig 504—Sagittal section of a male pelvis showing the relation of the prostate to the urethra and its separation from the rectum by Denonvillier's fascia

4 The *inferior pedicle*, usually formed by a single trunk, follows a downward direction on the anterior surface of the prostate until it reaches the perineal floor. There it reaches the internal pudendal artery where it follows its trajectory to terminate in one of the hypogastric nodes near the origin of this artery

The lymphatics of the prostate also anastomose with the lymphatics of the bladder fundus, the seminal vesicles, the ampulla of the ductus deferens, and the rectum. There are also intercalating lymph nodes behind the prostate and between the prostate and the rectum, but the lymphatics of the prostate for the most part are drained by the external iliac, the hypogastric, and the sacral lymph nodes (Fig 505)

## Chapter XII

# CANCER OF THE MALE GENITAL ORGANS

### CANCER OF THE PROSTATE

#### Anatomy

The prostate gland is situated at the level of the initial portion of the male urethra. Although it seems to be a part of the urinary system, it belongs physiologically in the male genital system. The prostate is divided into five lobes. The posterior lobe is that portion of the gland lying posterior to a plane passing through the ejaculatory ducts. The anterior lobe consists of the tissue forming the roof of the urethra. The two lateral lobes are formed by the prostatic tissue lying between the anterior and posterior lobes. The median lobe is formed by the narrow strip of tissue which lies between the internal sphincter and the verumontanum and which forms the floor of the urethra (Kahler). The ejaculatory ducts pass downward and forward through the posterior portion of the prostate to open into the urethra.

The superior surface of the prostate faces the bladder, the inferoposterior surface faces the rectum, and the inferolateral surfaces lie on the levator ani. The urethra lies at the level of the junction of the anterior and medial thirds of the prostate.

The prostate is enveloped in a tough pelvic fascia continuous with the upper fascia of the urogenital diaphragm which is anchored to the pubis by strong ligaments. The posterior portion of the prostatic fascia is called the *fascia of Denonvillier* and it forms an effective barrier between the prostate and the rectum (Fig 504). The capsule of the prostate is separated from this fascia by the prostatic plexus of veins communicating with the deep dorsal vein of the penis and vesical plexus and finally draining into internal iliac veins. This plexus also communicates with the vertebral vein plexus. Within the same area is a very abundant network of nerves derived from the hypogastric plexus. Some of these nerves run laterally toward the iliac vessels and come in close proximity to the bones of the pelvis. Another group passes along the peripheral soft tissues toward the sacrum and lumbar spine. The arterial supply of the prostate comes from the inferior vesical and middle hemorrhoidal branches of the hypogastric artery.

**Lymphatics**—The lymphatics of the prostate arise from the glandular veins and form a peridubular network. These lymphatic vessels increase in caliber as they near the capsule and in this subcapsular area they form a dense network. They are most abundant in the posterior and superior surfaces. This network of lymphatics is drained by four major collecting trunks (Rouviere) which follow the arteries of the prostate.

1 The *external iliac pedicle* is formed by a single trunk of lymphatics arising from the base of the prostate and from the upper part of its posterior surface. This trunk follows along the internal aspect of the seminal vesicle and then

Young found that in 800 patients with carcinoma of the prostate, the rectal mucosa was involved in only twelve instances. Local vessel and nerve invasion are common because of the location of the plexus between the capsule and the fascia. As the tumor continues to spread, it involves the seminal vesicles but seldom affects the urethra. Invasion of the bladder is a late phenomenon, but, if present, then partial or complete block of both ureters with secondary hydro-nephrosis and pyelonephritis can occur. Prostatic stones are only rarely associated with carcinoma. About 50 per cent of the patients with carcinoma have coincident benign prostatic hypertrophy. In thirty-eight autopsies reported by Graves, genitourinary complications were prominent. There was unilateral obstruction of the ureters in twenty-six instances and bladder invasion in sixteen. A significant degree of pyelonephritis was present in twenty-eight and it was the most common immediate cause of death.



FIG 510—Photomicrograph showing perineural sheath invasion by an adenocarcinoma of the prostate (low-power enlargement)

**METASTATIC SPREAD**—The lower lumbar spine, pelvic bones and upper femora are the commonest sites for metastatic disease which reaches these areas through the vertebral vein plexus (Fig 508). However, perineural invasion of lymphatics is also exceedingly common, and bone involvement of continuity or embolism resulting from direct invasion of marrow spaces of the cortical ostia (Warren). The overall majority of the cases show bone involvement but the majority with the thorax.

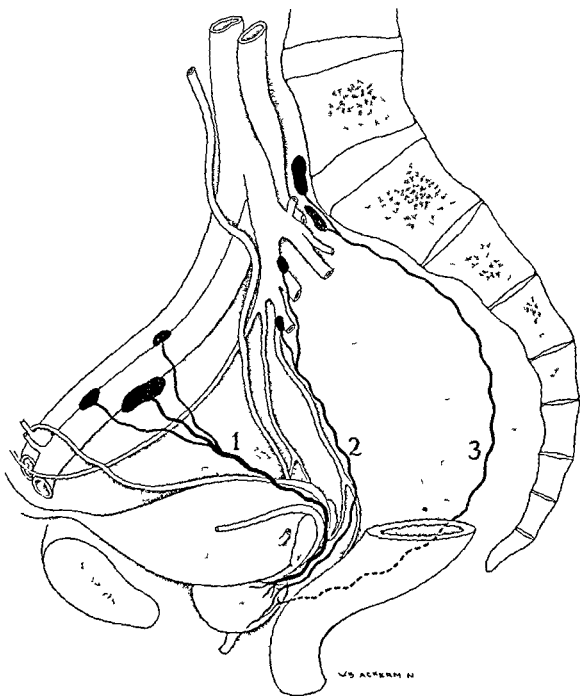


FIG. 505.—Schematic representation of the lymphatics of the prostate showing 1 external iliac pedicle 2 hypogastric pedicle and 3 posterior pedicle. The inferior pedicle which follows a downward direction and ends in hypogastric nodes is not illustrated here.

Fig 513

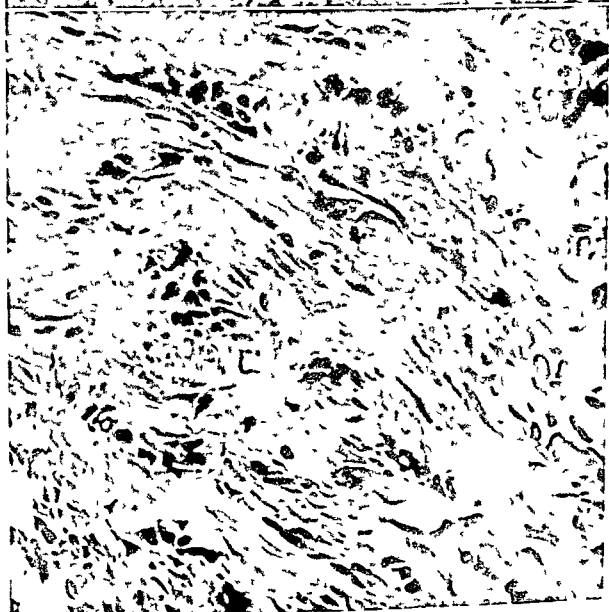
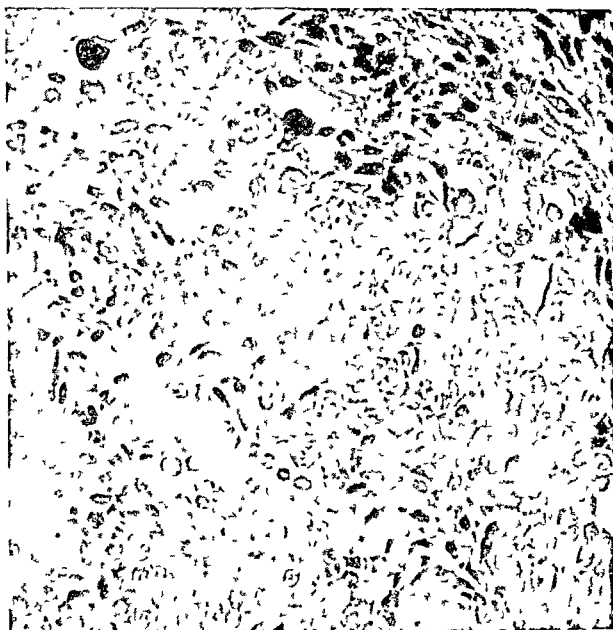


Fig 514

Fig 513 —Photomicrograph of a well-differentiated adenocarcinoma of the prostate

Fig 514 —Photomicrograph of the same tumor two years following bilateral orchiectomy  
Note fibrosis obliteration of many acini and nuclear changes

the examination. In the thirty-eight post mortem examinations reported by Graves, fourteen showed tumor in the lung and nine in the liver. Metastases to the lung are often of the lymphangitic variety. All but five had lymph node involvement particularly of the iliac, supraclavicular, peribronchial, aortic, and mediastinal nodes. Sarcomas of the prostate metastasize freely to the lungs and liver.

Fig 511



Fig 51

Fig 511—Photomicrograph of a well-differentiated adenocarcinoma of the prostate (moderate enlargement).

Fig 51—Photomicrograph of a small-cell carcinoma of the prostate (moderate enlargement). This is the most common variety of carcinoma of the prostate.



be correlated with a good or bad response. It was thought by Huggins at one time that the poorly differentiated carcinomas did not respond clinically, but Nesbit (1942) could not substantiate this finding. The few reported cases of *sarcoma* of the prostate are primarily leiomyosarcomas, rhabdomyosarcomas and lymphosarcomas.

### Clinical Evolution

In early carcinoma of the prostate restricted to a single lobe (usually the posterior) and not associated with hypertrophy, there are usually no symptoms other than perhaps some form of dysuria. The initial symptoms of a large group tabulated by Young are as follows:

	PERCENTAGE
Frequency of urination (pollakiuria)	69
Difficult or painful urination	43
Pain	31
Complete urinary retention	3
Hematuria	3

The pain, due probably to perineural sheath invasion, is referred to the bladder and urethra, rectum and perineum, sacrum and gluteal region, and the legs. It often suggests sciatic pain and is eventually present in most cases.

Unfortunately, the symptoms and signs which are present at first examination are often due to metastases. In 120 patients reported on by Graves, 81 had metastases (mostly bone) when first seen. With further extension of the tumor there may be partial occlusion of the rectal lumen and even rarely edema of the legs. Transverse myelitis can occur. Gross hematuria as the primary sign of cancer of the prostate was not found in any of the 1,000 cases reviewed by Bumpus.

The patients with advanced carcinoma of the prostate often become bedridden, develop a pronounced secondary anemia and have considerable pain. The tumor spreads to involve the bladder and signs of renal insufficiency are evident. Costovertebral tenderness and fever vary depending upon the degree of urinary infection. The usual immediate cause of death is renal insufficiency complicated by infection. *Sarcomas* of the prostate have a short clinical history; they rapidly become generalized.

### Diagnosis

**Clinical Examination**—The diagnosis of advanced carcinoma of the prostate is usually obvious. There is considerable pain with characteristic distribution and pronounced urinary symptoms. The symptoms, however, are often ascribed to arthritis or sciatica and consequently a rectal examination is omitted.

The physical examination of a patient with localized carcinoma of the prostate is negative except for the *rectal examination*, which reveals a poorly defined, nontender nodule most often located in the posterior lobe. In some instances, aspiration biopsy may be performed to make the diagnosis. In other instances, exposure by the perineal route and a subsequent frozen section may have to be done. With increase in the size of the tumor, the nodule becomes more diffuse and usually feels very firm. It often obliterates the normal architecture of the

**Microscopic Pathology**—Carcinomas of the prostate are adenocarcinomas which vary considerably in their appearance. The most common type is the small cell variety (Fig 512), but the cells may be larger with brightly staining eosinophilic cytoplasm and columnar epithelium. In certain instances the tumor can very closely resemble normal prostatic tissue. Moore (1935) has stressed the fact that each acinus of the normal prostate is surrounded by a fine band of collagenous connective tissue, and with the onset of carcinoma this limiting zone is lost. Perineural sheath involvement, which is extremely common (Fig 510) may be a means of definitely identifying a well differentiated carcinoma when the microscopic diagnosis is in doubt. The small cell type of carcinoma tends to invade and metastasize more quickly than the well differentiated type. Fat is commonly present but Gannor believes this is not a degenerative process for it often lies within the lumen of the carcinomatous alveoli and at times is seen as droplets within the cytoplasm. Microscopically islands of metaplastic epithelium can be confused with cancer.

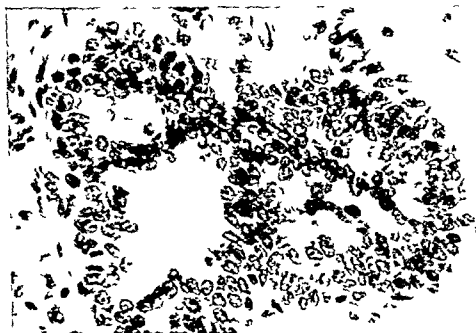


Fig 515—Photomicrograph showing intraductal hyperplasia of the breast following stilbestrol therapy in an aged male (moderate enlargement)

Prostatic carcinoma changes its microscopic appearance after orchiectomy or stilbestrol therapy. The tumor often becomes smaller, and individual tumor cells show shrinkage with diminution of cell cytoplasm and sometimes rupture (Figs 513 and 514). Pyknosis of nuclei and loss of nuclear details occur (Schenken). These changes can also be seen in the metastases. Skin metastases have completely regressed under therapy. The breasts become enlarged, their stroma somewhat edematous and the ducts which previous to stilbestrol were atrophic, may show intraductal hyperplasia (Fig 515). Angrist found that the study of Sertoli's cells, seminiferous tubules and interstitial tissue of the testis did not reveal any changes which could be correlated with clinical response. Neither has study of the primary prostatic cancer shown any findings which could

prostate and extension may be felt into one or both seminal vesicles. After suprapubic prostatectomy for benign hypertrophy, it is not rare for a carcinoma to appear, undoubtedly arising in the remaining posterior lobe and bearing no relation to the previous benign hypertrophy (Moore, 1943). Relatively infrequent findings are the presence of involved inguinal and supraclavicular lymph nodes and, in a few instances, transverse myelitis. Pathologic fractures, particularly of femur, vertebrae and ribs may occur.

**Roentgenologic Examination**—A roentgenographic examination of the skeletal system of every patient with carcinoma of the prostate is indicated, with particular attention being given to the most common areas of metastases (pelvic bones, sacrum, lumbar spine, femora, dorsal vertebrae and ribs). Of 539 patients examined by Bumpus, 123 showed involvement of the pelvis and 107 of the

TABLE XXXVI DISTRIBUTION OF METASTASIS FROM CARCINOMA OF THE PROSTATE AS DETERMINED BY ROENTGENOLOGIC EXAMINATION  
(After Graves, R. C. and Miltzer, R. F. J. Urol. 1935)

ONES OF ORGANS INVOLVED	NUMBER OF CASES	PERCENTAGE
Pelvic bones and sacrum	69	57
Lumbar vertebrae	18	79
Dorsal vertebrae	19	27
Cervical vertebrae	3	1
Femora	28	35
Ribs	18	22
"Shoulder girdles"	11	11
Humeri	4	5
Skull	1	1
Lungs	7	9

vertebrae. Bone metastases are invariably osteoplastic but can be mixed and rather infrequently are osteoblastic. Table XXXVI shows the common distribution of these metastases. The metastatic areas may regress under stilbestrol therapy or after orcheectomy (Figs 516 and 517), show increased density with bone repair or show both regression and progression in the same case under androgen control therapy.

**Laboratory Examination**—The most significant laboratory examination is the acid and alkaline phosphatase. Phosphatases are enzymes which in vitro catalyze the separation of phosphoric acid from phosphoric esters. Two enzymes, acid and alkaline phosphatase, are recognizable; the former has optimum activity at a pH of 5, and the latter at a pH between 8.5 and 9.5. *Acid phosphatase* is produced in the prostate gland of the adult. Gutman (1936) observed that tumor cells arising from prostatic epithelium retain the capacity to elaborate this enzyme. Unfortunately, the serum acid phosphatase is not elevated until tumor has extended beyond the prostate. When the test for serum acid phosphatase is performed with a proper meticulous technique (the King-Armstrong method), the upper level of normal is 3.5 K.A. units. Gutman (1940) found that the acid phosphatase was elevated in 85 per cent of 177 patients with pathologically verified suspected metastatic prostatic carcinomas. He stated that when the level is over 10 K.A. units, metastases must be present. This test is specific because no other condition is known which will produce such an elevation. A

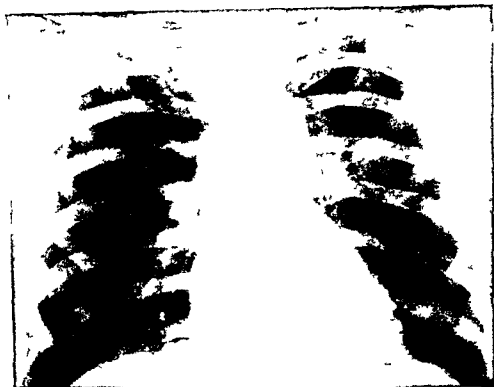


Fig 516—Roentgenogram of the chest showing spherical metastasis close to the hilum and overlying the left third rib anteriorly

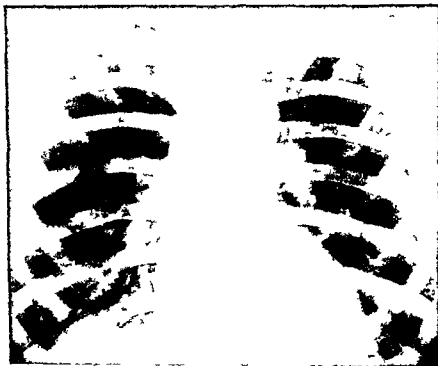


Fig 517—Roentgenogram of the same patient three months following bilateral orchiectomy. The metastatic lesion of the lung has completely disappeared

ied by Dean there was a decrease of estrogen output following castration and the level of 17-ketosteroids became elevated in eleven patients, in one there was no change, and in five the level of ketosteroids fell. Cause for this rise in eleven patients is as yet undetermined, but there is a question as to how much of the 17-ketosteroids represents an active element. It is possible that with the removal of the testes then inhibiting effect on the anterior pituitary is removed, which causes a stimulation and production of 17-ketosteroids from extragonadal sources such as the suprarenal gland. In nine patients treated with stilbestrol, the estrogen levels rose, and the 17-ketosteroids output fell in 100 per cent of the cases.

**Biopsy**—Before beginning treatment of an advanced carcinoma, there should be a positive biopsy. If the cancer has originated in the posterior lobe, the disease would have to spread over a considerable distance before a positive cystoscopic biopsy could be obtained. It is therefore logical to obtain tissue by an aspiration needle or a Silverman needle (Pearson). Material obtained by this method is frequently adequate, but if it does not reveal cancer, it has no significance.

**Differential Diagnosis**—With a hard prostate, pain, a demonstration of bone metastases by roentgenologic examination, and a high acid phosphatase, the diagnosis of advanced cancer of the prostate is unequivocal.

The differential diagnosis between *prostatic hypertrophy* and carcinoma may be difficult, for the symptoms of each entity frequently coexist. If the carcinoma is localized, then the indurated nodule can be a small area of infarction, a calculus, or a localized zone of hypertrophy. It is unfortunate that in early carcinoma the acid phosphatase is not diagnostic.

The most important differential roentgenologic diagnostic problem is that of *Paget's disease*. If the skull shows the typical changes of Paget's, then the other bone lesions are probably due to the same process. In Paget's disease, there is a bowing of the long bones without cortical thickening and without reduction of marrow spaces. Rib lesions are usually due to metastatic carcinoma. It is also possible for the two conditions to coexist. In osteoblastic metastases and in Paget's disease, the alkaline phosphatase is elevated. If the acid phosphatase is also elevated, then the bone changes must be due at least in part to metastatic carcinoma from the prostate. In a relatively few instances, roentgenologic examination may not suffice to make the diagnosis and a rectal examination and biopsy may become necessary (deVries). Primary *adenocarcinomas of Couper's gland* are extremely rare and are confused with carcinoma of the prostate (Gutiérrez). The primary symptom is pain in the rectum and perineum with a perineal tumor mass.

Primary *carcinoma of the seminal vesicles* is extremely rare (McNally), the seminal vesicles are frequently secondarily invaded by carcinoma, but it is most unusual to find definite proof of primary involvement with a normal prostate (Lyons). With primary carcinoma in the vesicles, there is lower urinary tract obstruction, pelvic pain, and hematuria. Rectal examination reveals a large, nodular, firm mass in the region of the seminal vesicles.

rather large number of patients with cancer of the prostate presenting definite metastases have borderline figures between 3 and 10 K A units of acid phosphatase in the serum (Gutman, 1942) This test should, therefore, be used in all patients before any therapy is instituted, for if the acid phosphatase is significantly elevated, metastases are present whether they can be seen roentgenologically or not Acid phosphatase can be used as a diagnostic measure for obscure bone lesions

The *alkaline phosphatase* is also frequently elevated when metastases to bone are present However, increase of alkaline phosphatase represents a nonspecific response to bone injury, bone growth, or attempts at bone repair, and consequently osteoblastic metastases cause elevation, but the serum alkaline phosphatase may be normal with osteolytic metastases It is elevated with Paget's

TABLE XXXVII CORRELATION OF SERUM ACID AND ALKALINE PHOSPHATASE DETERMINATIONS IN 159 CASES OF CARCINOMA OF THE PROSTATE GLAND  
(After Emmett, J L, and Greene, I F J A M A, 1945)

ACID PHOSPHATASE	ALKALINE PHOSPHATASE	CLINICAL EVIDENCE OF METASTASIS	
		PRESENT	NOT PRESENT
Elevated	Elevated	69	3
Elevated	Normal	17	1
Normal	Elevated	18	3
Normal	Normal	26	26
Total (159 cases)		126	33

Normal values Acid phosphatase 0 to 3 K A units per 100 c c alkaline phosphatase 0 to 10 K A units per 100 c c

disease Table XXXVII shows the relation between these two enzymes in a group of 159 cases It can be seen in this table that the acid and alkaline phosphatases are usually both elevated when metastases are present, but it should also be noted that in a certain number of cases the acid and alkaline phosphatases are normal, even in the presence of clinical evidence of metastases

The effect of androgen control on acid and alkaline phosphatases whether it be by orchiectomy or stilbestrol, is interesting Following castration, the acid phosphatase falls precipitously within the first twenty four to forty eight hours The alkaline phosphatase rises during the first four months because of new bone formation As Woodard points out after four to six months the serum alkaline phosphatase in castrated patients reflects the clinical course rather closely If metastatic areas undergo healing or remain stationary, the alkaline phosphatase is often normal If, however new metastatic areas appear, or old ones again take on activity the serum alkaline phosphatase rises again Following administration of stilbestrol the same changes occur except that they are somewhat slower in their evolution The injection of androgens causes further elevation of the serum acid phosphatase (Huggins, 1941)

The study of estrogen and 17 ketosteroid levels with carcinoma of the prostate is interesting but so far the results have been somewhat perplexing The 17 ketosteroids are probably a group of heterogeneous chemical substances of unknown biologic activity, identified by specific chemical reactions and produced mainly by the suprarenal cortex and the testis In seventeen cases stud

formed before there is clinical evidence of metastases prevents their later appearance. In executing the orchiectomy, Clute recommended, for psychologic reasons, that an intracapsular operation be done. By using this technique, the spermatic cord, epididymis, and an oval mass formed by the sutured tunica albuginea remain. Huggins gives additional estrogen therapy only for short periods of time to relieve hot flashes. If there is a recurrence of symptoms after orchiectomy, then stilbestrol may be given, but patients who benefit from it are few. Altea believes that the best form of therapy is orchiectomy followed immediately by diethylstilbestrol. He reasons that if the testes are removed, the anterior lobe of the pituitary may be released from inhibition by the testis and that the pituitary will then become overactive and stimulate the suprarenal cortex to produce androgenic hormones. By giving stilbestrol, this effect would be somewhat counteracted. Some urologists believe that bilateral orchiectomy should be delayed until metastases can be recognized, and then stilbestrol should be given only if improvement does not occur.

Stilbestrol is, for the most part, used to complement orchiectomy. It is also primarily used for those few patients who refuse orchiectomy, but some few authors advocate it as a primary form of therapy. The response to stilbestrol is slower than orchiectomy but similar to it. There may be unpleasant side effects with nausea and vomiting, painful and enlarged breasts, an accumulation of fat about the hips, and a tendency of the body to take on feminine contours. Toxic hepatitis can occur following large doses of diethylstilbestrol (Wattenberg). The proper dosage of stilbestrol is not known, but only infrequently do large doses result in a better response than small doses.

In summary, a definite statement cannot be made as to what form of androgen control should be used on nonoperable cases. Neither can any definite advice be given as to the time this control should be instituted. We feel that Huggins has given the most reasonable opinion. For the benefit of clarity, but with no thought that this represents the final decision, we recommend therefore (1) bilateral orchiectomy on all patients whether they have clinical evidence of metastases or not, (2) administration of stilbestrol in small doses when castration causes hot flashes and other symptoms, or when recurrence of symptoms appears, (3) administration of stilbestrol as a primary form of treatment in relatively small doses only to those who refuse orchiectomy.

*Clinical Response to Androgen Control*—The response of patients with advanced carcinoma of the prostate to androgen control is often spectacular. With castration changes occur within the first twenty-four to forty-eight hours, while with stilbestrol they are somewhat delayed. Amelioration of pain often quickly occurs, enabling bedridden or disabled patients to walk. Appetite is regained with resultant increase in weight. In advanced carcinoma, anemia is marked, but this anemia disappears under androgen control without benefit of iron therapy. Many patients return to normal activity.

In many instances there is gradual but definite regression and softening of the tumor. By rectal examination it may be difficult to verify that a carcinoma ever existed. The most striking results occur in the regression of the soft tissue extensions and lymph node metastases. Lymph nodes replaced by

### Treatment

**SURGERY**—If carcinoma of the prostate is ever to be cured, it has to be radically resected while it is still localized within the prostate. All other treatment is palliative. Unfortunately, the number of cases suitable for surgery is small (less than 5 per cent in most clinics). Young has been the most prominent protagonist of surgery for early carcinomas of the prostate. Approximately 20 per cent of the cases of carcinoma of the prostate seen at his clinic were suitable for operation, this high percentage was undoubtedly due to his prominence as a surgeon and the fact that many early cases were referred to his institution. Young emphasized that the operation must be radical and that any compromise procedure results in a high percentage of local recurrences and ultimate failure. He insisted on a *radical perineal prostatectomy with removal of the prostatic capsule and the fascia of Denonvillier, the vesical neck, much of the trigone, both seminal vesicles, and the ampulla of the vas deferens*. The defect is closed by drawing the bladder to the membranous urethra. The operative mortality is low. In 184 patients operated on by the staff of the Brady Urological Institute there were only twelve deaths (Young, 1945).

One of the main objections to this operation could be the supposed impairment of urinary control, but in sixty-nine cases analyzed by Colston, fifty patients had good urinary control, eleven fair control, and only eight poor control. The operation is not suitable for any patient with advanced disease or with evidence of distant metastases. Neither is it indicated when the patient is in poor general condition, for he is a poor operative risk.

In many instances the presence or absence of carcinoma cannot be determined by physical examination. The tumor should then be exposed by perineal approach and a frozen section diagnosis made. If there is no evidence of tumor, then the wound should be closed, but if a definite carcinoma is discovered then the radical operation should be carried out. When a frozen section diagnosis is inferable then the wound should be closed until a paraffin section diagnosis can be made.

**RADIOTHERAPY**—The implantation of radon seeds in the primary tumor and the administration of roentgentherapy to bone metastasis for the relief of pain are no longer used because of the far greater efficiency of androgen control.

**ANDROGEN CONTROL**—Androgen control means either the elimination of testicular androgen production by *orchectomy* or its neutralization through the administration of *estrogens*. The exact mechanism of the action of stilbestrol is not known. Huggins (1945) emphasized that prostatic cancer can become independent of androgens, basing this conclusion on evidence obtained when the suprarenal glands were removed in men who had had a relapse after *orchectomy*. Life was supported by adrenal substitution therapy. The androgens in these cases were not being formed but the carcinomas still followed an unfavorable course.

As soon as the diagnosis of cancer of the prostate is made, a bilateral *orchectomy* is the most widely accepted treatment (Merz). From an analysis of all reports it appears that the most dramatic effects occur with *orchectomy*, either immediately or delayed, but there is no evidence that *orchectomy* per



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## CANCER OF THE TESTIS

### Anatomy

The testes are formed by glandular tissue and convoluted tubules surrounded by connective tissue containing the interstitial cells of internal secretion. The testis is completely invested in a dense membrane, the tunica albuginea, which sends radiating septa into the gland. The tubules converge at the hylum or mediastinum testis, known as the *rete testis*, from which point a single convoluted tubule further extends to form the epididymis (Fig 518).

In the process of its descent from the abdomen into the scrotum, the testis develops several coats of tissue, the most significant of which is the tunica vaginalis, which nearly surrounds the testis except at the point where the epididymis is attached. Surrounding the vaginalis successively are the fibrous, muscular, and cellular layers, all of which are included in the dartos and the scrotum (Fig 519). There is a virtual cavity between the visceral and parietal layers of the vaginalis.

**Lymphatics**—The lymphatic network of the testis is complicated by the fact that there are not only primary channels but also secondary ones. The primary lymphatic drainage from the testis connects directly with the abdominal aortic lymph nodes extending from the bifurcation of the aorta up to the level of the renal pedicles. Lymph drainage from the epididymis goes to the external iliac nodes (Fig 520) and at times there may be drainage from the testis itself to one of these nodes located on the external right iliac vein just anterior to the point where the ureter crosses the vein. Lymph nodes draining the right testis lie between the left renal vein and the inferior mesenteric artery. Beyond these channels, secondary lymphatics on both sides of the aorta communicate with each other. In 90 per cent of the cases, moreover, there is a lymph channel ascending above the renal veins connecting the mediastinal



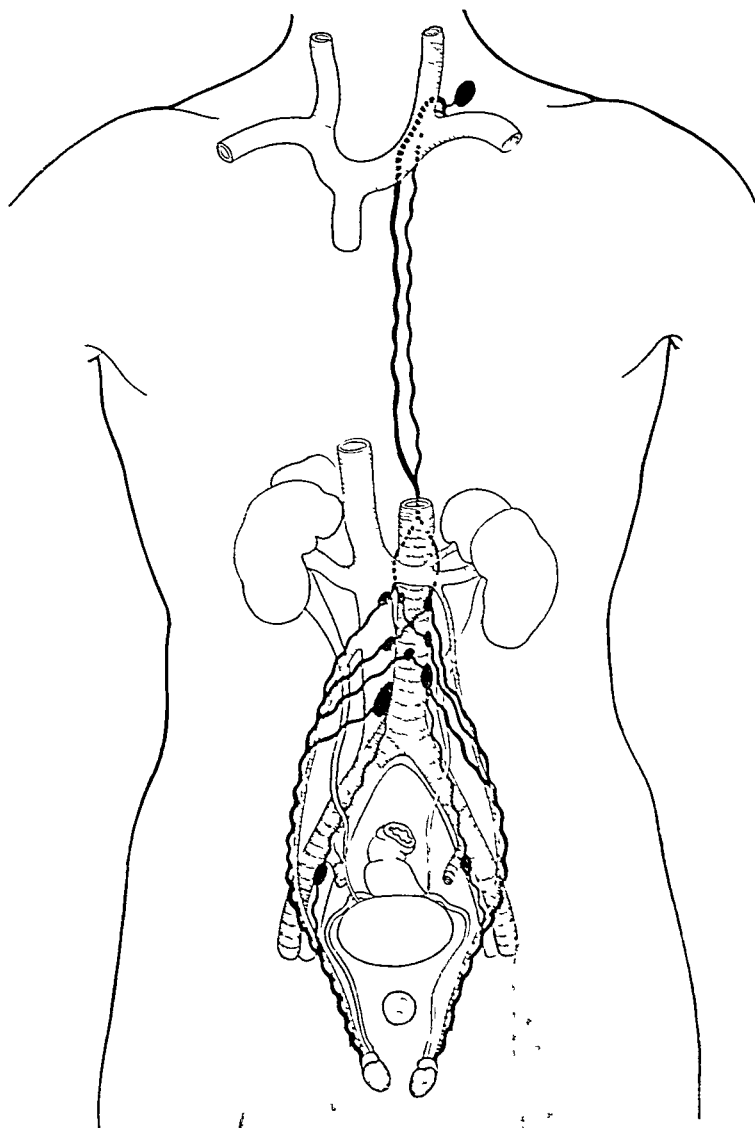


Fig 520 —Schematic repr  
in the para-aortic lymphatics and  
left supraclavicular node is filled  
into the external iliac lymph node

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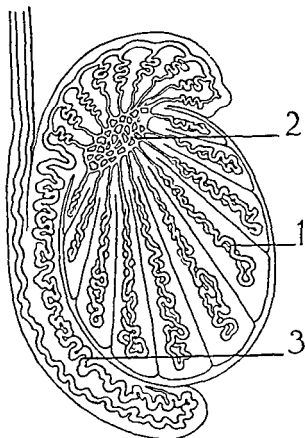


Fig 518 —A schematic representation of a section of a normal adult testis showing 1 convoluted tubules 2 rete testis and 3 epididymis

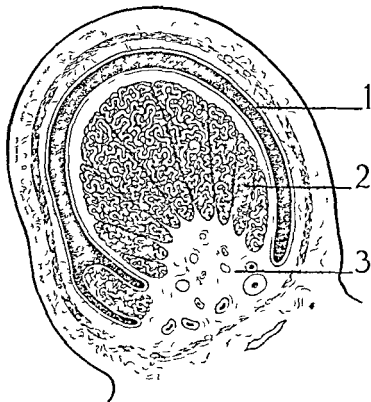


Fig 519 —Cross section of a normal adult testis showing 1 tunica vaginalis 2 convoluted tubules and 3 rete testis.

tumor of the testis had occurred. It is interesting that one of every eight of Pen-son's patients had an abnormally retained testis, a figure which is far in excess of the normally expected incidence of retained testis (0.005 per cent).

Cryptorchidism may possibly be related to an abnormal influence of steroid substances such as estrogens, for in animals bilateral cryptorchidism is characterized by an excessive secretion of gonadotropins. In rodents the nondescended testis functions abnormally and reacts peculiarly to androgens and to gonadotropins (Hamilton, 1938). In other experiments, teratomas of the testis of the fowl have been induced by injections of zinc chloride. While these tumors usually appear in the spring at the height of sexual activity, they can be produced at other times of the year if the zinc chloride is combined with extracts of anterior pituitary (Michalowsky, Bagg).

### Pathology

**Gross Pathology**—Tumors of the testes arise possibly from some vestigial mesonephric structures in the region of the rete testis, the area between the testis and epididymis. Ewing showed that all tumors of the testis are teratomas arising from totipotent sex cells in the neighborhood of the rete. These tumors can be classified as follows:

	INCIDENCE (%)
Teratoma (adult type)	5 to 10
Embryonal carcinoma (seminoma or embryonal carcinoma with lymphoid stroma)	60 to 70
Adenocarcinoma	25 to 30
Choriocarcinoma	1 to 2
Miscellaneous rare types	1 to 2

Chevassu felt that the seminoma was a specific type of tumor arising from the epithelium of the seminal tubules. Ewing, however, believed that the seminoma simply represented an overgrowth of one type of cell—a monodermal development of a tumor primarily interdermal in origin. In support of this thesis, Manei showed that six of seven seminomas showed more than one type of tissue. This concept is the more widely acknowledged. From the practical standpoint, nevertheless, treatment of seminomas remains the same no matter what the histogenesis.

Testicular tumors vary greatly in size; they may enlarge the organ to ten times the normal dimensions or may be occult in a normal-sized testis. The tumor itself is usually fairly firm, depending upon cellularity, bone, cartilage, and connective tissue content. A cross section of the adult teratoma shows cystic spaces, mucinous areas, cartilage, and bone formation (Fig. 522). However, if these tumors are less differentiated, they are softer and often develop areas of hemorrhage and necrosis. The choriocarcinoma is usually small, hemorrhagic, and soft. The embryonal carcinoma or seminoma is customarily homogeneous, noncystic, pinkish yellow, only occasionally showing areas of hemorrhage and necrosis (Fig. 523).

Benign tumors of the testes, such as fibromas, adenomas, leiomyomas, and interstitial-cell tumors, do occur but are seldom encountered. Only about twenty

nodes The intercostal nodes in turn drain to the juxtavertebral and thence into a prevertebral plexus which may drain into the jugular and subclavian confluence or into the left supraclavicular lymph nodes

### Incidence and Etiology

Testicular tumors compose less than 1 per cent of all malignant tumors The majority occur in patients 20 to 40 years old The greatest incidence is found in patients 29 to 34 years of age, during which period they are the most common malignant tumors found in males (Dorn) The highest incidence of the teratoma occurs at the average age of 28 years and that of the so called seminoma at 40 years (Fig 521)

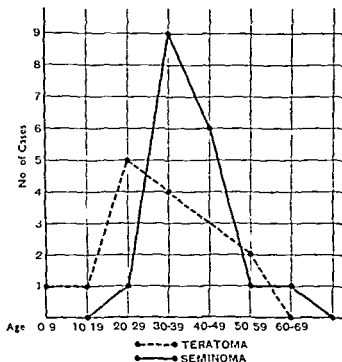


Fig 521—Diagram of age incidence illustrating the more frequent occurrence of seminomas at a later age (From Gordon Taylor G Brit J Urol 1938)

There is no evidence to support the concept that syphilis or other inflammations bear any etiologic relation to the development of testicular tumors Trauma probably serves only to draw attention to an already present tumor Twelve per cent of testicular tumors occur in undescended testes Inguinal undescended testes are four times more common than abdominal undescended testes, and yet one in about twenty abdominal testes shows malignant change in comparison to one in eighty inguinal testes This fact gives further support to the belief that trauma is probably not an important factor in the production of malignant change in the inguinal testis, which because of its location is fairly accessible to injury (Campbell)

After a patient has had one of these rare tumors the chances of his developing another are statistically far greater than those of a normal man (Hamilton, 1942) Pearson collected 46 cases of teratoma in which a second

six interstitial-cell tumors of the testis have been reported. These tumors are usually yellowish brown in color and are well delineated (Nation, Wairen). Tumors of the spermatic cord, epididymis, and testicular tunics are extremely rare. The majority of these tumors are benign (Thompson, Hinman, 1924).

The direct extension of testicular tumors is limited somewhat by the tunica albuginea, which, if encroached upon, may show surface nodules. Further extension beyond the tunica albuginea is rare but tumors may proceed to involve and even ulcerate the skin of the scrotum.

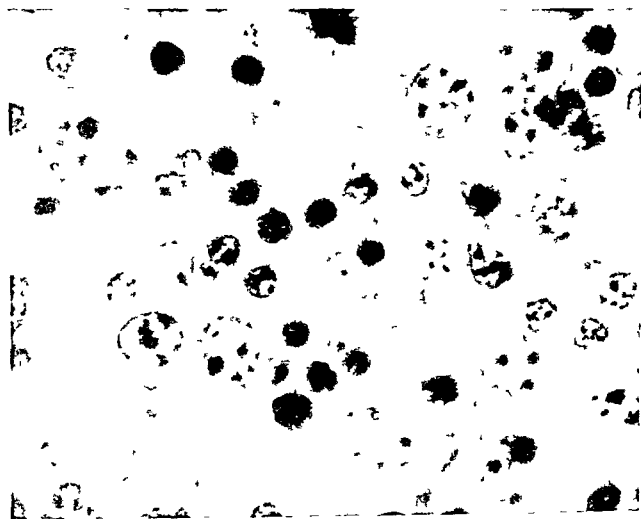


Fig 524.—Photomicrograph of a testicular seminoma showing characteristic large clear cells with rather fine nucleoli. Lymphoid stroma is present (high-power enlargement).

**METASTATIC SPREAD**—The complicated lymphatic network leading from the testis allows frequent extensive invasion of the body. Barringer (1941), reporting thirty-seven cases that came to autopsy, found lymph node involvement in 60 per cent and lung metastases in 78 per cent. Moreover, in 75 per cent of the cases with lung involvement, the liver was also affected, but this invasion of the liver occurs through the blood after the tumor has invaded the lung. Distant node involvement is also to be expected. Barringer (1941) found that 27 per cent of his patients presented metastatic disease from the bifurcation of the aorta up to the left supraclavicular region. This latter group invariably had a continuous chain of metastatic nodes along the course of the thoracic duct, and it was from these affected duct nodes that disease spread by direct extension to the higher region. Barringer also discovered that retroperitoneal node involvement was frequently bilateral.

At times, the left renal pedicle can be obstructed when nodes draining from the right testis are involved, because these nodes lie between the left renal vein and the inferior mesenteric artery. If tumor has involved the epididymis, then

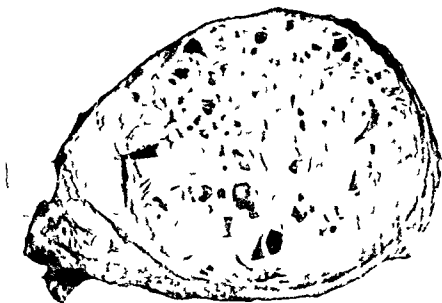


Fig 52<sup>o</sup> —Photograph of a gross specimen of an adult teratoma with characteristic cystic spaces  
A remnant of normal testis can still be seen

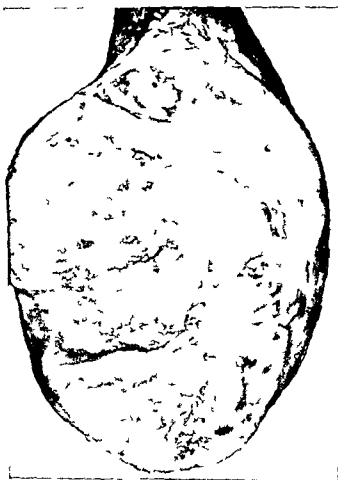


Fig 53 —Gross appearance of a seminoma of the testis with characteristic zones of necrosis



scopically, there is so-called choriogenic gynecomastia comprising bilateral breast enlargement, colostium production, and pigmentation of the nipples. These changes may disappear after orchiectomy.

Usually the clinical symptoms and findings are related to the primary tumor. Metastatic disease is only rarely the first symptom. The inguinal nodes are involved only after the tumor has broken through its capsule or when small fragments of tumor are left embedded in an operative wound. Enlarged retroperitoneal lymph nodes induce lumbar pain radiating down the leg, symptoms of ureteral obstruction, or constipation. The urinary symptoms may result in costovertebral tenderness, dysuria, vomiting, and anorexia due to increasing nonprotein nitrogen (Table XXXIX). Pulmonary metastases may cause cough, dyspnea, pleural pain, and infrequent hemoptysis due to secondary invasion of the bronchus by involved lymph nodes.

### Diagnosis

**Clinical Examination**—The testis, no matter its size, outwardly retains a normal shape. The tumor is well delineated, painless, and firm, with a clean cut line of demarcation at the upper limits. The epididymis is flattened on its posterior surface and is seldom involved by tumor. In 15 per cent of the cases the tumor is accompanied by a hydrocele. The fluid may be aspirated in order to palpate a tumor. A hydrocele can be mistaken for tumor, but its fluid extends upward to the base of the penis without any clear boundary line and the penis appears shortened or retracted. Its clear liquid allows easy transillumination which is best carried out in a darkened room by means of a small flashlight. Solid structures like tumors, syphilitic gummas, and calcified hematomas do not transilluminate and consequently this examination is of great assistance in determining the clinical diagnosis.

The abdomen should be carefully examined for retroperitoneal lymph node metastases. The examination can be best made when the legs of the patient are slightly flexed on the abdomen, the arms by the side, and the patient breathing through the mouth (Fig 525). Palpation must be fairly deep, the metastatic nodes usually lying at the level of or slightly caudad to the umbilicus. The left supraclavicular node area should also be investigated. Metastases within the lung are scarcely ever detected on physical examination unless they are very large, approach the pleura, or compress or invade the bronchi. Infrequently rectal examination may reveal involvement of periprostatic lymph nodes (Baringer, 1944).

**Roentgenologic Examination**—Retrograde (rather than intravenous) pyelograms are invaluable for demonstrating retroperitoneal lymph node metastases and should be taken routinely for all tumors of the testis before treatment is begun. If negative, they provide a comparison for future examinations. Because of the lymphatic drainage, node involvement can cause partial or complete high obstruction of one or both ureters. In these circumstances the ureter is displaced laterally (Fig 526), the outer limits of the psoas muscle are rounded as though the muscle were contracted, and the lumbar vertebrae

the lymph node drainage will extend to the external iliac lymph nodes. Spread also travels through the spermatic veins either to the renal vein on the left or directly into the inferior vena cava on the right. Even bone involvement has been recorded although it is infrequent, and rare cases have been reported with tridermal metastases (Adams). If ulceration or invasion of the tunica albuginea occurs, then involvement of inguinal lymph nodes is to be expected. The only other time when these nodes may become involved is when tumor is left in a wound and develops in the subsequent scar.

**Microscopic Pathology**—Microscopically, the adult teratoma shows all types of tissue, with elements traceable to mesoderm, ectoderm, and entoderm. It is important to notice whether with step or serial sections zones of undifferentiated tumor are revealed in an apparently well differentiated tumor, for this finding may alter the prognosis. The choriocarcinomas present large multinucleated giant cells with a syncytial stroma. The embryonal carcinomas or seminomas have cells quite uniform in appearance with eosinophilic cytoplasm, fairly prominent nucleoli and abundant mitotic figures. Lymphoid stroma is variable (Fig 524). The adenocarcinomas show well formed acini with occasional papillary formation. At times it is not infrequent to find some areas suggesting choriocarcinoma.

### Clinical Evolution

Tumors of the testes generally develop slowly, relentlessly, and insidiously. As they grow, their weight alone may produce discomfort or even lumbar pain, and testicular sensitivity decreases. At times these tumors may evolve rapidly and progress mercilessly to metastases and death which may occur six to eight months after the first symptom. Dean found that in 66 per cent of his patients the average length of time from the first symptom to examination was four months with another six and one half month delay before treatment was started. Rarely in the choriocarcinoma or cases in which its elements are present micro

TABIE XXXIX RELATION OF SYMPTOMS TO LESIONS DUE TO METASTATIC SPREAD

Involved inguinal nodes	Tumor growing through tunica albuginea or tumor growing in operative scar
Lumbar pain Constipation Pain in scrotic distribution	Involvement of retroperitoneal nodes
Cotovertebral tenderness Lumbar pain Irritation Dysuria	Partial ureteral or renal pedicle obstruction by involved nodes
Vomiting Headache Drowsiness	Impending renal failure due to block of ureters or renal pedicle by involved nodes
Cough Dyspnea (may suggest tuberculosis)	Involvement of lung and mediastinal nodes
Hemoptysis	Involved bronchial or tracheal nodes eroding, tracheobronchial tree
Cerebral symptom	Brain metastases
Swelling of lower extremity	Inferior vena caval obstruction by lymph node metastases

metastatic disease after orchiectomy a high hormonal excretion is prognostically significant. Diminution of hormonal excretion after therapy is started does not necessarily indicate a good prognosis. It should be remembered that castration increased intracranial pressure and orchitis may also increase hormone excretion.

**Differential Diagnosis**—*Tuberculosis* which is invariably primary in the epididymis results in nodularity and may cause 'beading' of the vas deferens. Only in the late stages however does extension into the testis take place. With tuberculous involvement of the testis other portions of the genitourinary tract and lungs may be affected but this can usually be demonstrated by clinical and roentgenologic examination. Roentgenograms of the testis showing calcification in the region of the epididymis is presumptive evidence of tuberculosis.



Fig. 32.—Roentgenogram after catheterization of ureters showing lateral deviation of the left ureter by para-aortic adenopathy.

Further aid in diagnosis can be gained from roentgenograms of the lung which will show any tuberculosis present or by palpation of the prostate which may reveal evidence of nodular caseous tuberculosis. Pulmonary symptoms from metastatic cancer of the testis may result in an erroneous diagnosis of tuberculosis.

*Syphilitic gumma* of the testis is today only rarely observed because of the present improved methods of its treatment. If it should appear it may be extremely difficult to differentiate from a tumor of the testis because it is

show a wedging with convexity toward the affected side (Fig 527) *In men between 20 and 40 years the presence of pulmonary metastases as shown roentgenologically is frequently due to a primary carcinoma of the testis*

**Hormone Studies**—Hormone studies have a diagnostic value as well as an ability to evidence metastases. Ferguson felt that the histologic type and the radiosensitivity of the tumor could be predicted by the amount of hormone excreted. Twombly, on the other hand, believed that the quantity of hormone in the urine did not reveal either its histologic structure or necessarily its radiosensitivity but found that when the hormone excretion was low, the tumor was less malignant than when it was high. Patients with 1,000 units had 77 per cent survival, those with 1,000 2,000 had 43 per cent, those with 2,000 5,000 had 18 per cent, and none of those with over 10 000 units survived. The production of corpora lutea in the test animals also had an ominous significance. In

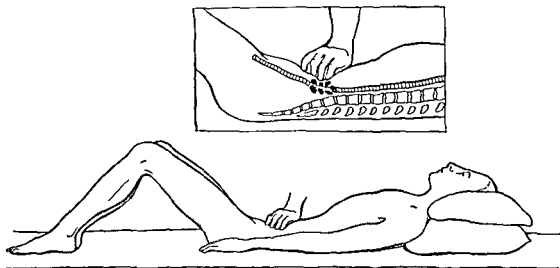


Fig 5 3—The palpation of deep retroperitoneal lymph nodes can best be accomplished when the patient is lying in a recumbent position with the head supported and thighs flexed

general the adult teratomas had low titers, the seminomas very variable titers and the choriocarcinomas high titers. It should be emphasized that even when metastases are present the titer may be very low except with the choriocarcinomas. Sometimes the hormone tests may be completely negative but a high positive hormonal output after orchiectomy usually indicates metastases. Hydrocele fluid can be used for the Aschheim Zondek test. Laqueur emphasizes that the qualitative estimation of hormone excretion and the biologic assay of testicular tumors are of value. He feels the presence of the chorionic hormone is of the greatest importance and that in certain instances it may result in interstitial cell hyperplasia. He further states that if follicular stimulating hormone alone is present, it may have no relation to any functional activity of the testicular tumor. He therefore emphasizes that the routine histologic study of testicular tumors should be supplemented by biologic analyses.

Certainly quantitative and qualitative hormone studies as modified by Twombly should be done to diagnose obscure cases. Besides indicating occult

syphilitic gummas may also displace and destroy the organ as they grow within it. The surgical removal of the testis also submits the entire specimen (unaltered by irradiation) for pathologic study. At operation the spermatic cord should be exposed and clamped at the external inguinal ring before the testis is removed. Exploration of the testis during this procedure should be avoided because of the possibility of spread of tumor resulting from this manipulation.

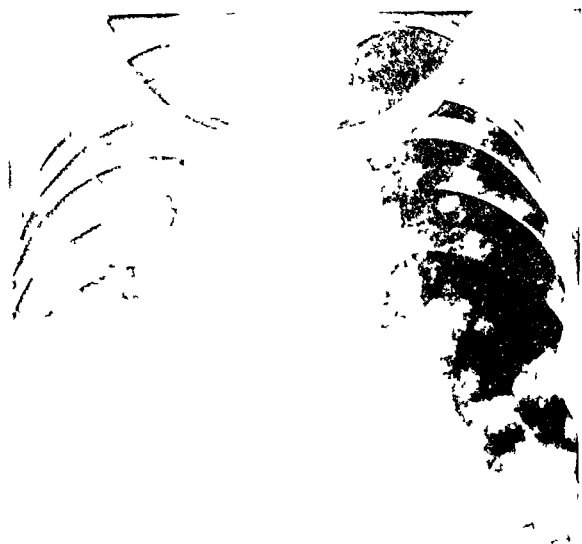


Fig. 28.—Numerous mediastinal and pulmonary metastases from a seminoma of the testis.

In the treatment of malignant tumors of the testis, however, an orchiectomy alone yields rather poor results. Tanner reported only 6 per cent four-year survivals following orchiectomy alone. This low percentage probably represents the number of adult teratomas without metastases present in the treated group. A radical dissection of the retroperitoneal lymph nodes as advocated by Chevassu and popularized by Hinnman (1923, 1942) is no longer felt to be of value and has now been abandoned even by its most enthusiastic advocates. If the nodes are not involved, the operation is valueless and, conversely, if they are implicated, the retroperitoneal dissection will be insufficient. For these reasons, postoperative radiotherapy over the region of possible lymphatic spread is always indicated after orchiectomy.

**RONTGEN THERAPY**—The administration of *preoperative* radiotherapy to the testicular tumor has not been shown to be of value and, in addition, it usually modifies the architecture of the tumor and interferes with its proper pathologic study. The knowledge of the pathologic entity being so vital to the future

sharply differentiated and fairly firm. The serology, however, will be positive and other stigmas of syphilis may be present. These changes, nevertheless, should not rule out the possibility of coexisting syphilis and tumor.

Spontaneous hemorrhage into the testis can occur and, because *hematoceles* do not transilluminate, they may easily be mistaken for tumor. In addition, the hematocele may be very firm if organization of the clot has taken place. Trauma often precedes a hematocele. Simple *orchitis* is seldom confused with a testicular tumor because of its evident elements of acute inflammation.

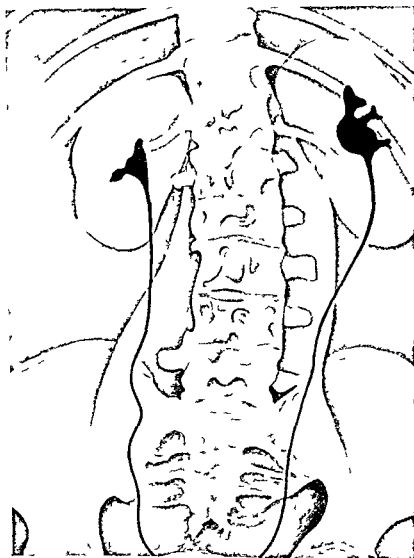


Fig. 57—Sketch of a roentgenogram of retrograde pyelography illustrating the deviation of the left ureter by an enlargement of para aortic nodes wedging of the lumbar spine with convexity toward the left side as well as changes in the contours of the psoas muscle.

### Treatment

**SURGERY**—Orchectomy is indicated for all tumors of the testis. Even if the clinical diagnosis of malignant tumor is not certain, no biologic loss is sustained by the surgical removal of the testis because benign tumors and

of retroperitoneal metastases, the same procedure allows 40 per cent five-year survival. It should be added, however, that recurrences after five years are not uncommon. Cabot and Berkson showed that an appreciable number of patients who had lived five years without disease had a recurrence before ten years, but the majority of recurrences develop within the first year after treatment. Rosenblatt described a case of a 29-year-old patient on whom orchiectomy without benefit of postoperative radiotherapy was done. Eleven years later retroperitoneal nodes appeared and roentgentherapy was administered. A recurrence in these lymph nodes another eleven years later finally caused death. Table XL illustrates the results which may be expected with the best form of treatment.

TABLE XL RELATIVE PROGNOSIS OF DIFFERENT TUMORS OF THE TESTIS

HISTOLOGIC TYPE	PROGNOSIS	APPROXIMATE FIVE YEAR SURVIVAL WITH OPTIC THERAPY AND POSTOPERATIVE RADIO THERAPY
Seminoma without metastases	Excellent	75
Seminoma with metastases	Fair	40
Adult teratoma without metastases	Excellent	80
Adult teratoma with metastases	Hopeless	0
Adenocarcinoma without metastases	Fair	40
Adenocarcinoma with metastases	Poor	15
Teratoma in retained testis with metastases	Poor	Less than 5
Choriocarcinoma with metastases	Hopeless	0

The size of the tumor and the duration of the disease apparently have little prognostic significance. If the lymphatics of the cord or the periprostatic lymphatics are involved by tumor, the outlook is grave (Barringer, 1944). Tumors arising in undescended testes have a poor prognosis because they are diagnosed late. Kocher found no cures in a series of fifty-five such cases.

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welfare of the patient, we believe that roentgentherapy should never be administered before orchiectomy. On the other hand, *postoperative roentgentherapy* is of great value in improving the results of the simple orchiectomy, particularly with seminomas and adenocarcinomas but is not indicated after the surgical removal of adult teratomas which make up less than 10 per cent of all testicular tumors. Irradiation is of no value in choriocarcinomas for, when first seen, widespread metastatic disease is invariably present. These tumors metastasize very frequently and their metastases are not as radiosensitive as those of the less differentiated tumors of the testis. In seminomas and adenocarcinomas postoperative roentgentherapy is always indicated *whether there is clinical evidence of metastases or not*. The radiotherapy should be directed to both sides of the midline because of the frequency of contralateral metastases particularly at the level of the renal pelvis. Irradiation through abdominal fields is most commonly used but dorsolumbar fields may be added with advantage.

When clinical evidence of retroperitoneal metastases is revealed by palpation or pyelograms the possibility of mediastinal involvement is greater than 50 per cent. It should be remembered that lack of roentgenologic evidence of mediastinal involvement does not mean that metastases are not present. In these cases an additional course of roentgentherapy directed to the mediastinum may be of great value and while it would not imply any important risk it would be amply justified.

Seminomas are by far the most radiosensitive of testicular tumors, and voluminous retroperitoneal lymph nodes and even lung metastases may disappear after irradiation. Whether the disappearance of the metastatic lymph node is permanent or temporary depends greatly on the method and technique of the radiotherapy which is given. That a metastatic seminoma of the lymph nodes can be sterilized was pathologically proved by Prunswick.

A close follow up of all patients for at least every 6 months is warranted. Repeated roentgenograms of the chest, hormone excretion studies and intravenous pyelograms may reveal new evidence of disease after surprisingly long remissions but when treated early may increase considerably the life expectancy of the patient.

### Prognosis

A good prognosis may be given to the *adult teratomas* because of their slow development and late metastases. However when metastases occur the prognosis is poor for they are usually uncontrollable by surgery and radiotherapy. Teratomas which show areas of adenocarcinoma have only a fair prognosis because they more frequently metastasize to the retroperitoneal lymph nodes. The *choriocarcinomas* invariably present a dismal outlook when first seen and death usually occurs within a year in spite of radiotherapy. *Adenocarcinomas* of the testis have a very variable prognosis depending on their degree of radiosensitivity. *Seminomas* have the best prognosis of all testicular tumors. When the disease appears clinically confined to the testis and is treated by orchiectomy and postoperative roentgentherapy to the potentially metastasizing areas, 50 per cent of the patients survive five years. When there is clinical evidence of



in the preputial sac the skin of the penis changes to a mucous membrane which, reflecting beyond itself, covers the glans. Numerous glands of the sebaceous type, the Tyson's glands, are found in the prepuce and mucosa of the penis.

**Lymphatics**—The lymphatics of the *prepuce* spring from a network which covers both its internal and external surfaces. They converge toward the dorsal aspect, join with the lymphatics coming from the skin of the shaft, and form several trunks which run toward the pubis, ending in the upper inner group of superficial inguinal lymphatics.

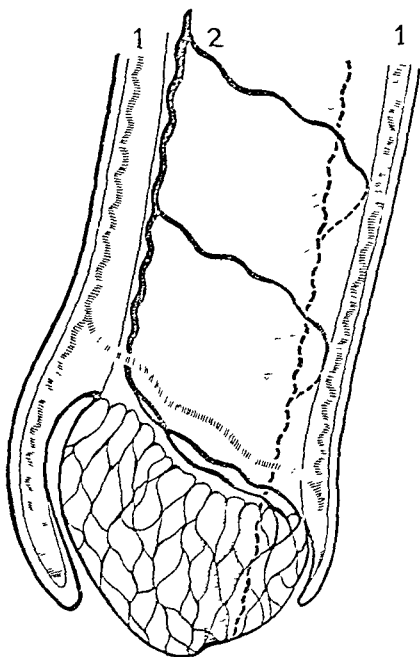


FIG. 329.—Anatomic sketch of the lymphatic network of the penis gathering in 1 subcutaneous trunks and those of the glans drained by 2 a subfascial trunk.

The lymphatics of the *glans* form a very rich network which runs toward the frenulum. There they communicate with the lymphatics of the urethra and form several collecting trunks which follow the retroglandular sulcus forming a collar of lymphatics that entirely surrounds the corona and finally forms one two, or three trunks which run along the dorsal surface of the penis under the penile fascia and together with the deep dorsal vein. Arriving at the suspensory ligament, these trunks form a presymphyseal plexus with multiple anastomoses and occasional nodules. From here the lymphatic trunks are divided into two groups, those which follow the *femoral canal* and end in the deep inguinal nodes, in the node of Cloquet, and in the retrofemoral nodes, and those that follow the *inguinal canal* which, running under the spermatic cord, end in the external retrofemoral lymph nodes (Cunéo).

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## CARCINOMA OF THE PENIS

### Anatomy

The penis is a cylindrical organ formed by three tubes of fibrous tissue. Two of these tubes the corpora cavernosa are symmetrical and are next to each other on the anterior midline. The third the corpus spongiosum, contains the urethra and runs posteriorly in a groove between the two corpora cavernosa. The corpus spongiosum ends anteriorly on a coniform expansion, the glans at the summit of which is found the external urethral orifice. The base of the glans is marked by a prominent margin the corona, above which is the retro glandular sulcus. Each one of the three cavernous bodies is encased in a fibrous sheath the tunica albuginea, and the three are all enclosed in a common fascia which is surrounded by the subcutaneous tissue and the skin. Anteriorly the skin and subcutaneous tissue have a prolongation, the prepuce, which normally covers the glans. A small midline fold, the frenulum passes from a point immediately behind the external urethral orifice to the deep surface of the prepuce.

The skin which covers the penis is remarkable for its thinness and elasticity. Sebaceous glands are found throughout. The dermis is entirely lacking in smooth muscle fibers and contains only connective and elastic tissue fibers. Deep

The lymphatics of the *corpora cavernosa* end in the superficial upper and inner group of inguinal lymph nodes and sometimes also in the deep inguinal nodes and retrofemoral nodes. The lymphatics of the *urethra* and of the *corpora cavernosa* usually end in the deep inguinal lymph nodes.

Little is known of the lymphatics of the erectile bodies but that they lead to the superficial and deep inguinal nodes. It should be emphasized that the left and right inguinal lymph nodes have a rich communication with each other through the subcutaneous lymphatics.

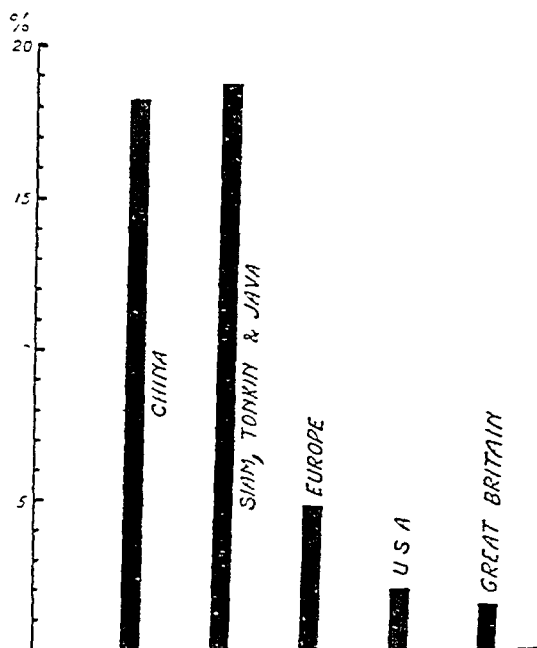


Fig. 531.—Differences in frequency of carcinoma of the penis in men of different countries expressed in percentages of total cancer in males. (From Ngai S. K., *Am. J. Cancer*, 1935)

### Incidence and Etiology

The incidence of carcinoma of the penis varies greatly in the different countries of the world (Fig. 531). In Europe and in the United States carcinomas of the penis make up at the most 5 per cent of all carcinomas found in the male, whereas in Asia the incidence rises to 20 per cent, reaching its maximum in China, Siam, and Java. In Europe and in the United States these lesions are mostly found in patients 40 to 70 years of age, while in the East they are found in men 35 to 54 years old. In 108 cases of carcinoma of the penis in Americans, Dean found twenty-four (22 per cent) in patients under 40 years of age, while Ngai in 106 cases in Chinese found forty-four (41 per cent) in patients less than 40 years old.

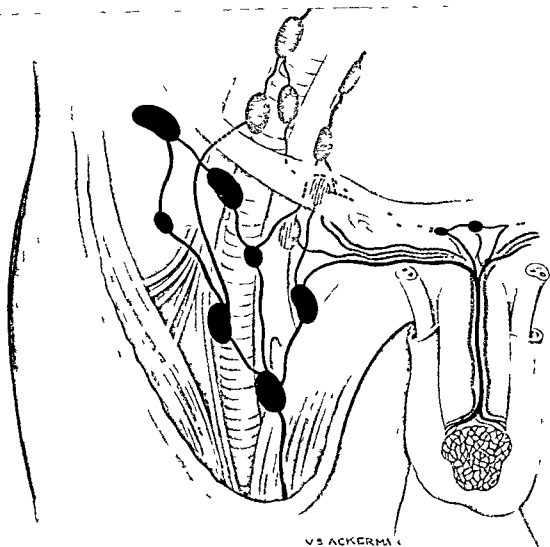


Fig 530 — Anatomic sketch of the lymphatics of the penis. A rich network of lymphatics gathers in several trunks which run toward the symphy is where they form a presymphysal plexus. From there the lymphatic trunks divide in two groups: those following the femoral canal which terminate in the superficial lymph nodes (solid black) and those following the inguinal canal which terminate in the deep lymph nodes (shaded).

in order to determine if the excision has been adequate. *Erythroplasia* is characterized by hyperplasia of the epithelium, thickening of the rete, and ulcers either single or multiple. These ulcers are surrounded by red scaly dermatitis (Melnick). Bowen's disease, also a precancerous lesion, shows the histologic appearance of epidermoid carcinoma in situ.



Fig. 332.—Well-delineated relatively early carcinoma of the glans.

### Clinical Evolution

Very often the first symptom of carcinomas of the penis is a small nodule, warty growth, vesicle, or superficial ulceration, often painless, growing under an unretreated prepuce and consequently overlooked until it reaches considerable size. Rarely the first symptom is a metastatic inguinal lymph node. As the lesion progresses, there is usually spontaneous bleeding, and secondary infection usually adds an offending odor. When there is coexisting phimosis

This form of cancer is extremely rare in the circumcised Jew and only one instance has been reported (Wolbarst, Dean). Also, in India, it rarely occurs in Mohammedans, who are ritually circumcised between 4 and 9 years of age, while it is commonly found in the uncircumcised Hindu. It has been thought that the balanitis resulting from irritation by the smegma bacillus in the presence of phimosis or long redundant prepuce is one of the main predisposing causes of carcinoma of the penis. In forty two of the fifty nine patients reported on by Demarquay, phimosis was present. In all countries, however, this form of cancer is found in men of the lowest economic level with sordid living conditions and habits. A certain racial immunity may, in addition, be invoked in the case of the Jew similar to the immunity of Jewish women to carcinoma of the cervix.

*Syphilis* may rarely be a factor in the causation of carcinoma, a few instances of tumor arising in a scar of a chancre having been reported. *Trauma* is not among the etiologic factors. *Erythroplasia of Queyrat*, a rare disease of the glans is a definite precancerous lesion.

### Pathology

**Gross and Microscopic Pathology**—Carcinoma of the penis may arise frequently on the glans, the retroglanular sulcus, the prepuce and rarely from the skin of the shaft.

The gross appearance of the lesion may be either proliferative or ulcerative. The *proliferative type* first appears like a small wart, followed by the appearance of other nodules which coalesce to form numerous papillary projections (Fig 532). Sometimes this tumor reaches a huge size, completely replacing the entire penis (Fig 533). These exophytic tumors rarely invade the corpora cavernosa or the urethra but are usually accompanied by considerable secondary infection.

The *infiltrative or ulcerative type* is more common than the proliferative and grows inwardly, destroying the glans and the prepuce (Fig 534). Not infrequently they invade the corpora cavernosa and urethra, and contact lesions in the form of satellite nodules may grow on the prepuce and glans at the same time.

**METASTATIC SPREAD**—Inguinal metastases are rarely found in the proliferative type of lesions. Demarquay reported only two cases with metastases in a series of 112 patients with the proliferative type. The ulcerative type of lesion metastasizes more readily. Large metastatic inguinal nodes can become fixed, ulcerate through the skin, erode underlying vessels and cause profound hemorrhage. The vertebral vein plexus may rarely serve as a means of metastases. Distant metastases to abdominal nodes, liver, and lungs can occur.

The microscopic appearance is that of a squamous carcinoma which in the proliferative type often is very well differentiated. The ulcerative infiltrative type tends to be more undifferentiated. In the microscopic examination of surgical specimens particular attention should be paid to gross evidence of involvement of the urethra and corpora cavernosa and to microscopic evidence of perineural extension. Sections should be taken at the limits of the excision.

edema of the glans and of the prepuce may rapidly increase. Rarely is there any dysuria. It is only after metastases have developed that any constitutional symptoms are evident. About 30 per cent of the cases present inguinal metastases at the time of the first clinical observation (Tailhefer). In late cases the metastases to inguinal nodes will become fixed and infected and can even ulcerate through the skin. Infrequently the large underlying vessels may be eroded and profound hemorrhages can occur. At times, widespread metastases will contribute to the cause of death. Terminal infections such as bronchopneumonia are common in this group because of age and general debility.

### Diagnosis

For a thorough examination of the glans, a surgical division of the prepuce may be warranted. This may facilitate the examination of an early carcinoma hidden within the preputial sac. The diagnosis of a typical proliferative or ulcerative growth presents no difficulties. There should be no hesitation in removing a specimen from the borders of the lesion for a pathologic diagnosis. It is often difficult to ascertain whether the inguinal nodes are involved or not for they are frequently enlarged by inflammation, but when the nodes are larger than 3 cm in diameter they are usually metastatic. An aspiration biopsy of enlarged inguinal lymph nodes or a surgical excision of one of these nodes for pathologic diagnosis is very often indicated in order to solve the treatment of these areas.

**Differential Diagnosis**—Benign *papillomas* may resemble an early carcinoma of the glans but although they have a tendency to grow together, they may present relatively wide normal spaces between them. *Condyloma acuminata* may also be confused with carcinoma, but these have a characteristic appearance, a long clinical history, and microscopically do not show any tendency to infiltrate (Buschke). There is no difficulty in differential diagnosis with a *syphilitic chancre*, but it should not be forgotten that a carcinoma may coincide with a primary syphilitic lesion and that in a suspicious lesion the demonstration of spirochetes does not preclude the taking of a biopsy. *Soft chancres* are usually tender and are accompanied by voluminous, painful inguinal adenopathy of the groin. Infected *sebaceous cysts* of the prepuce may occur and should be considered in the differential diagnosis. *Peyronie's disease*, a plastic induration of the penis, can be confused with carcinoma because of its firmness. This condition is accompanied by pain and distortion with erection and consequent interference with sexual intercourse. Infrequently calcification can occur. Radiotherapy has been reported to relieve this condition (Soland). *Erythroplasia* of the glans is characterized by its well-circumscribed, velvet, deep red appearance. It may become malignant.

### Treatment

Kennaway believes that circumcision in infancy prevents the development of carcinoma of the penis but that a circumcision done later is not equally prophylactic. There are two main considerations in the treatment of carcinoma of the

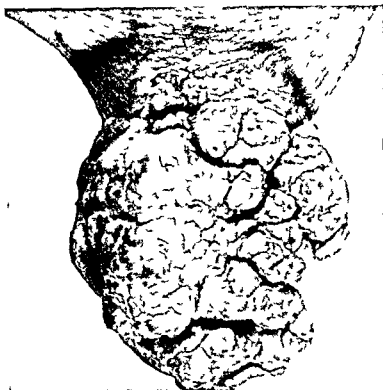


Fig 53—Advanced extensive proliferative well differentiated carcinoma of the p ni



Fig 54—Gross specimen of an advanced deeply infiltrating poorly differentiated carcinoma of the



on by Baringer in whom disease was confined to the penis, fifty-five were well between one and ten years after surgical treatment. Nineteen had passed the five-year period. Late recurrences are infrequent. Of twenty-six cases developing recurrences reported by Barney, only four appeared after the fifth year. After surgical excision of the primary lesion the more undifferentiated tumors and those which involve the corpora cavernosa, urethra, or show penile sheath involvement have a worse prognosis because of their tendency for deep lymph node metastases. The prognosis of these patients is directly related to the existence of involved regional lymph nodes and to the therapeutic procedure employed and the time of its institution. In thirty-seven cases with involved inguinal lymph nodes reported by Baringer, there were only nine patients living and only two of these were free from disease for more than five years. Of forty-nine patients of carcinoma of the penis treated at the Foundation Curie, fifteen had inguinal metastases. The local lesions were treated with radium and the metastases were surgically excised. The over-all result was 23 per cent five year survival (Tailhefer).

Of twenty-six cases collected by Taylor and Nathanson in which prophylactic and therapeutic inguinal dissection were done and positive nodes found, eleven of the patients had survived three years or longer.

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penis the treatment of the primary lesion, which, in general offers no difficulties, and the treatment of its metastatic adenopathy which involves often a question of judgment

### Treatment of the Primary Lesion —

**CURIETHERAPY** —Interstitial implantation of radium needles was abandoned soon after the first trials because of its poor results. Surface application of radium by means of radium molds however has been successful in sterilizing carcinomas of the penis but the procedure is rather delicate and requires unusual skill. It has the advantage of preserving most of the organ except the area which may have been destroyed by the tumor. It finds its best indications in early lesions.

**ROENTGENTHERAPY** —There have been few trials of roentgentherapy in the treatment of a primary lesion of the penis. On the basis of limited experience however there are reasons to believe that these tumors can be sterilized by external roentgentherapy with a minimum of resulting defect provided that irradiation is well protracted and that the radiations are of good quality.

**SUPPURY** —A partial or total penectomy is a very successful means of treating these lesions. When a surgical excision is undertaken however, a margin of safety of at least 15 cm. is required. With this margin of safety local recurrences are seldom observed.

**Treatment of the Metastatic Adenopathy** —A *therapeutic inguinal dissection* is of course indicated in all patients in whom there is certainty of an inguinal metastasis. In general all enlarged nodes which are more than 3 cm. in diameter may be assumed to be metastatic. Aspiration or incisional biopsy of smaller nodes will often contribute the certainty of their involvement. The dissection should be bilateral because of the subcutaneous lymphatic communications. Obviously an inguinal dissection will not be indicated in patients with distant metastases nor in those in whom the lymph nodes have become definitely fixed.

A *prophylactic inguinal dissection* is not always indicated but it may have a definite value in some cases. In relatively young patients with an undifferentiated carcinoma of the penis a bilateral inguinal dissection is justified in our opinion. A justifiable number among these patients will have microscopic metastases.

Roentgentherapy of metastatic inguinal lymph nodes is only justified as a palliative measure when surgery is not indicated. External irradiation of these areas with a curative purpose requires administration of large amounts of radiation through a single large field and thus is seldom compatible with the preservation of the normal tissue in this area. Obviously radiotherapy is of no value when applied routinely in small doses to the inguinal regions as a prophylactic measure.

### Prognosis

The prognosis of patients with carcinoma of the penis is very favorable when metastatic lymph nodes are not present. In sixty-three patients reported

on by Barringer in whom disease was confined to the penis, fifty-five were well between one and ten years after surgical treatment. Nineteen had passed the five-year period. Late recurrences are infrequent. Of twenty-six cases developing recurrences reported by Barney, only four appeared after the fifth year. After surgical excision of the primary lesion the more undifferentiated tumors and those which involve the corpora cavernosa, urethra, or show perineural sheath involvement have a worse prognosis because of their tendency for deep lymph node metastases. The prognosis of these patients is directly related to the existence of involved regional lymph nodes and to the therapeutic procedure employed and the time of its institution. In thirty-seven cases with involved inguinal lymph nodes reported by Barringer, there were only nine patients living and only two of these were free from disease for more than five years. Of forty-nine patients of carcinoma of the penis treated at the Foundation Curie, fifteen had inguinal metastases. The local lesions were treated with radium and the metastases were surgically excised. The over-all result was 23 per cent five-year survival (Tailhefer).

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## Chapter XIII

# TUMORS OF THE SUPRARENAL GLAND

### Anatomy

The suprarenal glands crescentic in shape, rest on the upper pole and medial border of the kidneys. The right suprarenal lies against the diaphragm posteriorly; its anterior surface is molded by the liver and inferior vena cava and it reaches the duodenum inferiorly. The left suprarenal gland is separated from the stomach by the omental bursa, and inferiorly it is crossed by the splenic artery and upper border of the pancreas (Fig 535). The right suprarenal vein drains into the inferior vena cava; the left descends to the left renal vein. Their arterial blood supply is abundant with branches from the inferior phrenic artery and aorta. The very numerous nerve fibers which innervate the suprarenal glands arise from the greater splanchnic and postganglionic vagal fibers from the celiac plexus.

Accessory suprarenal tissue is frequently found in the kidneys, in the perirenal and retroperitoneal fascia, and in the capsule of the liver. It may also be found in the broad ligament of the uterus attached to the pedicle of the ovary or associated with testicular tissue.

The suprarenal gland is divided into two portions, the cortex and the medulla, each of which has separate embryologic origins and is actually almost like two distinct organs. The cortex develops from the celomic mesoderm and the brownish medullary central portion arises from the ectoderm which gives rise to the sympathetic nervous system.

**Lymphatics**—The lymphatics of the suprarenal gland arise from the cortex and the medulla and collect into several trunks which follow the direction of the vessels. The collecting trunks which accompany the superior suprarenal artery end in lymph nodes situated near the origin of the celiac artery and the inferior vena cava. The collecting trunks which accompany the middle suprarenal artery end in the lateroaortic nodes placed above the renal pedicle. Those which accompany the suprarenal vein are divided into anterior and posterior trunks, ending also in lateroaortic nodes (Fig 536). In addition to these main trunks, some of the lymphatics of the suprarenal glands may pass through the diaphragm, following the splanchnic nerves, and terminate in a retroaortic node in the posterior mediastinum. Some of the lymphatics of the right suprarenal gland may penetrate into the liver (Rouviere).

### Incidence

Tumors of the suprarenal gland are not observed very frequently, inasmuch as they make up only a relatively small percentage of all tumors. Cortical *adenomas* are commonly found at autopsy, but those that are diagnosed during life and which produce symptoms are infrequently observed. *Adenocarcinomas* of the cortex occur considerably less frequently, Wu having found only eighty

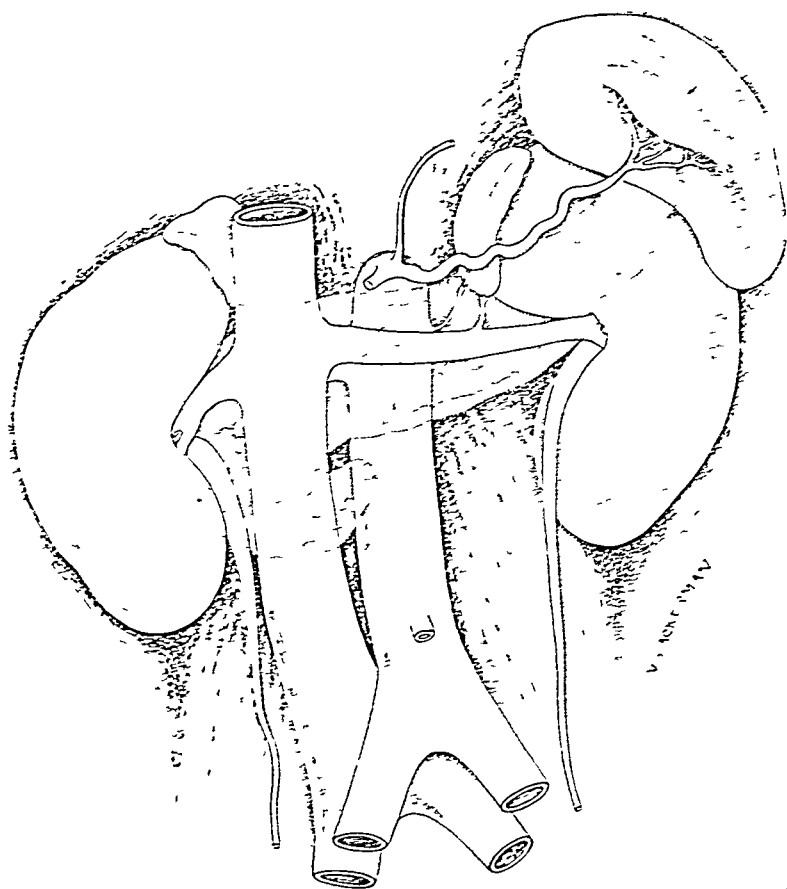


Fig. 535—Anatomic sketch illustrating the normal position of the supra-renal glands and their relationship to the vena cava on the right and the splenic artery and pancreas on the left.

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two cases in the literature from 1803 to 1940, they have been observed in children 1 to 5 years of age, most frequently in females, and are found equally in both sexes in adults 31 to 40 years of age (Glynn)

Benign tumors of the medulla are also pathologic rarities. McFarland found only ninety-three reported cases of *ganglioneuroma* of the suprarenal gland or accessory suprarenal tissue in a review of the literature from 1905 to 1931. They are observed in children and young adults.

*Pheochromocytomas* are most often observed in the fourth and fifth decades of life. *Neuroblastomas* which arise from the suprarenal medulla are the most common malignant suprarenal tumors. They are observed in children 15 to 3 years of age and constitute a rather important proportion of the malignant tumors which occur in childhood. Fairer (1940) found forty neuroblastomas in a series of 301 malignant tumors in children.

### Pathology

**Gross and Microscopic Pathology**—Tumors which develop from the adrenal cortex have an epithelial character, while those developing from the medulla are nervous system tumors. In order to facilitate their discussion, the following classification is adopted:

#### TUMORS OF THE SUPRARENAL GLAND

- I Tumors arising from the cortex
  - A Adenoma
    - 1 Functioning
    - 2 Nonfunctioning
  - B Adenocarcinoma
- II Tumors arising from the medulla
  - A Ganglioneuroma
  - B Pheochromocytoma (Paraganglioma)
  - C Neuroblastoma
  - D Mixed type

*Tumors Arising From the Cortex*—Although the origin of the cortical tissue is mesoblastic, the cells of the cortex acquire an epithelial character. Most of the tumors originating in the cortex are benign. The cortical *adenoma* is often bilateral and frequently found at post-mortem examination. As a rule these tumors are small, measuring from a few millimeters to several centimeters in diameter. They are well delimited and somewhat spherical in shape, showing a rather deep brown, homogeneous appearance (Fig 537). On microscopic examination the capsule of the adenoma is found to be formed of usually well-vascularized connective tissue and the individual cells resemble those of the normal cortex. The cells are arranged in cords or bundles and deposits of chromaffin pigment are often present. Goormaghtigh reported histologic differences in two tumors, one occurring in a feminized male and another in a virilized female. In cases in which a syndrome of pituitary basophilism is present, hyaline cells described by Crooke will be found in the anterior lobe of the pituitary.

*Adenocarcinomas* which arise from the cortex may also appear to be encapsulated but are usually larger than the benign tumors (4 to 15 cm and often over 500 grams in weight). These tumors usually show zones of hemorrhage and

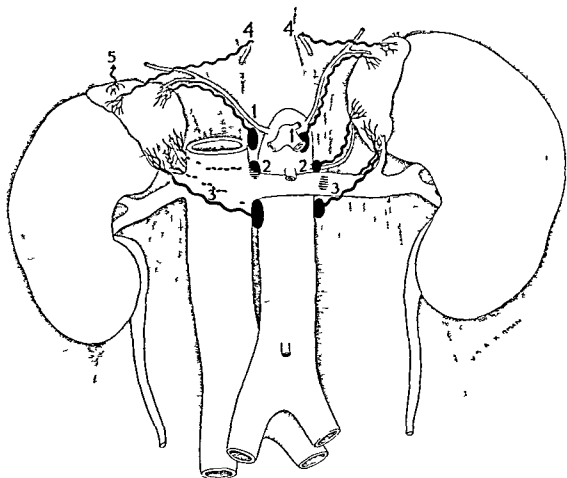


Fig 536 —Sketch of the lymphatics of the suprarenal glands illustrating their termination in the lateroaortic nodes 1 trunks which accompany the superior suprarenal artery 2 collecting trunks accompanying the middle suprarenal artery 3 collecting anterior and posterior trunks accompanying the suprarenal vein 4 lymphatics perforating the diaphragm and ending in posterior mediastinal nodes and 5 lymphatics leading directly to the liver



malignant tumors are usually small but may reach a size of 10 cm in diameter. As a rule they are encapsulated and soft, invariably showing zones of hemorrhage and of necrosis (Fig 539). They are sharply delimited, but as they increase in size they erode through the capsule, grow luxuriantly in the surrounding tissue, and invade veins but do not encroach upon the substance of the kidney. On microscopic examination, the neuroblastoma is made up of large numbers of cells with narrow rims of cytoplasm which resemble but are slightly

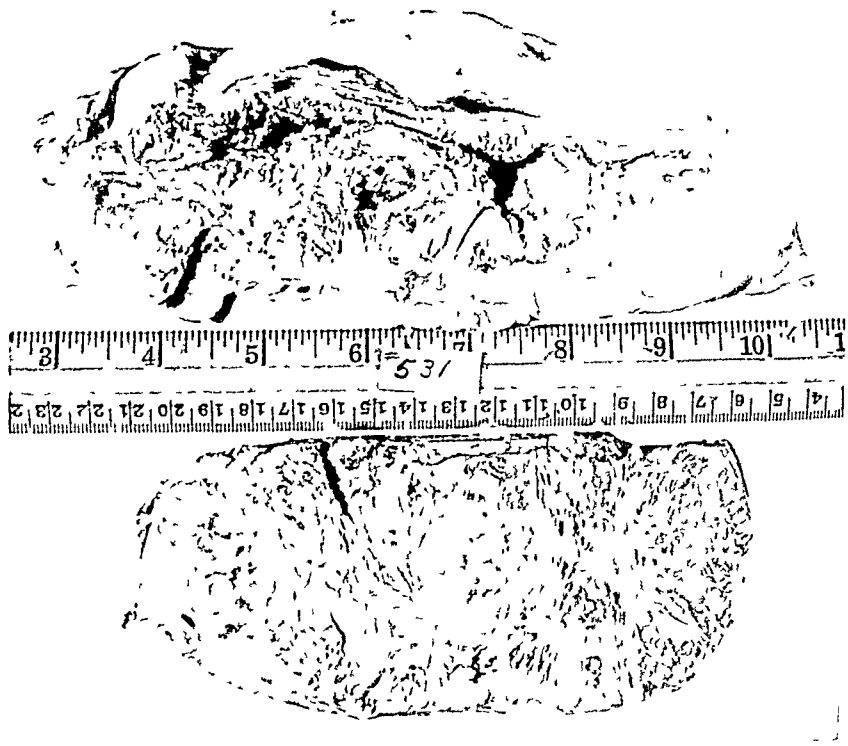


Fig 538—Bilateral adrenocarcinomas of the suprarenal glands each weighing over 1000 grams (Courtesy of Dr. John Saxton, Department of Pathology, St. Louis City Hospital, St. Louis, Mo.)

larger than normal lymphocytes. These tumors could easily be confused with sarcomas, but they can be differentiated because of the presence of "rosettes," which are formed by a concentric arrangement of the nuclei at the periphery of an indefinite mass of cytoplasm. The earliest stage of development of the rosettes is the formation of ball-like areas, the sympathoblasts forming more perfect rosettes than the sympathogonia (Blacklock). Although rosettes are often present in the primary tumor, they are often not seen in the peripheral metastasis.

## TUMORS OF SUPRARENAL GLAND

necrosis (Fig 538) They seem to occur more frequently on the left than on the right (Wu) The tumor may break through the capsule and invade the surrounding tissues On the right, tumor usually spreads directly to the liver but seldom invades the major veins On microscopic examination the tumor is often undifferentiated and individual cells show striking variation in size and shape There are numerous mitotic figures Areas may be found where various layers of the cortex can be recognized The adenocarcinoma may be difficult to differentiate microscopically from a malignant pheochromocytoma (rare) However, the presence of fat vacuoles within cells and the absence of brown pigment after fixation in chromate solutions or other oxidizing agents are signs in favor of cortical origin, while conversely, the absence of fat and the presence of pigment after chromate fixation are signs of a medullary origin (LeCompte) LeCompte emphasizes that histochemical methods and assay of fresh tissue for epinephrine and steroid hormones may give more definite information in the investigation of such tumors

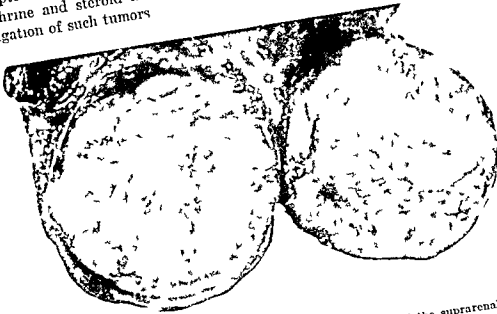


Fig. 537.—Typical encapsulated homogeneous cortical adenoma of the suprarenal gland

**Tumors Arising From the Medulla**—Tumors which arise from the medulla are of nerve origin The *ganglioneuroma* arises from and is almost entirely made up of mature ganglion cells This tumor is usually found only by chance in the region of the suprarenal gland The *pheochromocytoma* arises from the chromaffin cells or pheochromocytes and is composed almost wholly of medullary tissue but small nests of cortical cells may be present It tends to be encapsulated and may reach a diameter of 12 centimeters The tumor is usually of brownish color, showing cystic changes hemorrhage and necrosis It shows rather large cells which have an affinity for chrome salts It seldom shows evidence of fat by special stains Neurofibromatosis is, at times, associated with pheochromocytoma (Kirshbaum)

The most important group of tumors arising from the suprarenal medulla are the *neuroblastomas* which derive from the primitive neuroblasts These

from Zuckerkandl's organ. Malignant carotid body tumors and pheochromoblastomas are pathologic curiosities.

**METASTATIC SPREAD**—Malignant tumors of the suprarenal gland sometimes present markedly different forms of metastatic spread. The *adenocarcinomas* of the cortex metastasize predominantly to the liver, lungs, brain, and the regional nodes (Wu). Bone metastases are rarely observed.

Some *neuroblastomas* are characterized by a massive involvement of the liver and mesenteric lymph nodes without producing or at least very rarely giving any bone metastases (Pepper's type). Another type of *neuroblastoma* is characterized by the frequency of early metastases to the bones of the skull (Hutchison's type). It must be emphasized that these two clinical types are

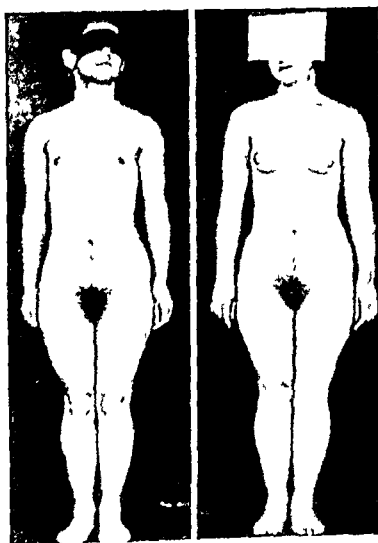


Fig. 511.—Girl 16 years of age with a virilizing suprarenal adenoma. On the right, the same patient four years after surgical removal of the tumor. Notice the unquestionable change in secondary sexual characteristics. (From Cullit & J. Surg., Gynec. & Obst. 1942)

not clear-cut. Few confirmed the presence of metastases to the skull in forty-seven of fifty-one neuroblastomas of the Hutchison type. It is probable that these metastases are related to the vertebral vein system. In addition to the skull metastases, metastatic implants are found in the sternum, vertebrae, ribs, and long bones. On microscopic examination the vertebrae reveal a preserved architectural pattern and the bone marrow appears in excessive amounts. In the long bones, subperiosteal extension with bone formation at right angles to the long axis is sometimes seen. In the skull, punched-out areas with complete destruction of the bone are often observed together with soft tissue masses invading and distending the orbital tissues. The metastases in the liver tend to be very diffuse, enlarging and almost completely replacing it.

*Mixed tumors*, presenting all transitions from neuroblasts to adult ganglion cells, are rarely observed. All of these transitions may be present in the same tumor and there have even been cases reported in which developmental stage of the sympathoblasts has manifested themselves as separate individual tumors (Wahl Dunn). Silver stains may be helpful in demonstrating nerve fibrils (Cajal).



Fig 539

Fig 539—Typical neuroblastoma of the suprarenal gland well delimited hemorrhagic and with extension into the renal pelvis

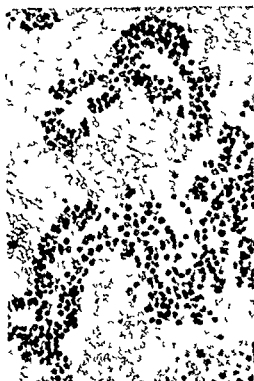


Fig 540

Fig 540—Typical rosettes are visible

Benign and malignant tumors showing the same character as those developing from the suprarenal medulla may arise from accessory suprarenal tissue found elsewhere. These tumors have been found arising from the paraganglionic tissue in immediate proximity to the suprarenal gland, in the celiac plexus, in the organ of Zuckerkandl near the bifurcation of the iliac vessels, in the root of the lung and in the superior cervical ganglion. The most important of these tumors are the *carotid body tumors*, which are paragangliomas (pheochromocytomas) usually found at the bifurcation of the common carotid artery and intimately associated with the cervical sympathetic trunk, the vagus, and at times the internal jugular vein. They are very rarely bilateral (Ranlin). Philips found eleven pheochromocytomas outside of the suprarenal gland, nine of which arose

gland may be associated with alterations of the metabolism, these alterations, however, may occur without tumor and may closely resemble pituitary basophilism (Cushing's syndrome). In this syndrome the following signs and symptoms as outlined by Haymaker are invariably combined

- 1 *Adiposity*, rapidly acquired, confined to face, neck, and trunk, tender suprascapular pads (Fig 542)
- 2 *Kyphosis* associated with spinal pains, osteoporosis usually, localized to spine
- 3 *Sexual dystrophy*, amenorrhea in females, impotence in males
- 4 *Hyperttrichosis* of face and trunk in females and preadolescent males, possibly the reverse in adult males
- 5 *Linea atrophica* dark red in color with dusky or plethoric appearance of skin
- 6 *Vascular hypertension*
- 7 *Erythremia*
- 8 *Abdominal pains, fatigability, ultimate extreme weakness*

Along with this variety of possible hormonal symptoms, adenomas of the suprarenal gland may become palpable and this, of course, greatly facilitates the diagnosis. In general, however, the diagnosis has to be made on the symptomatology.

**Adenocarcinomas**—Occasionally, malignant tumors of the cortex are the cause of hormonal alterations, and these changes can be as variable as in the adenomas (McGavack). Pain is frequently the first symptom produced by adenocarcinomas of the cortex, but even more often a mass becomes noticeable in one suprarenal area. With the development of metastases, weight loss and deterioration of the general condition become part of the clinical picture. Signs of suprarenal insufficiency are rare.

### **Tumors Arising From the Medulla—**

**Ganglioneuromas**—The evolution of the ganglioneuroma is slow and it seldom produces any symptoms other than those due to its increased size. In general it is discovered at autopsy.

**Pheochromocytomas**—The clinical evolution of the pheochromocytoma may be most dramatic and, once seen, is never forgotten. The tumor causes paroxysmal attacks due to intermittent flooding of the blood stream with pressor substances. There is sweating, weakness, facial pallor (encephalal), and tachycardia. Dyspnea, shock, nervousness, nausea, vomiting, giddiness, blanching, pallor of the extremities, precordial pain, and a sense of constriction of the chest may occur. These paroxysms may occur for many years, and the physiologic changes can be extremely alarming. In exceptional instances the vascular changes produced by the hypertension lead to severe involvement of the vessels of the retina, heart, brain, and kidney (Thorn) and, in some instances, may cause death. The attacks may occur following exertion, change in position, deep breathing, massage of the suprarenal area, or palpation of the tumor mass or may be simply produced by emotion. All the signs and symptoms of these paroxysmal attacks may be reproduced by an experimental injection of an overdose of adrenalin.

**Neuroblastomas**—Cases of a neuroblastoma occurring in utero have been the cause of fetal dystocia (Weinberg). In general this tumor has a rapid clinical course and may be found only at autopsy. There are two classical

Malignant pheochromocytomas with metastases have been reported but are extremely rare (King). The metastases of the mixed type of tumor invariably show only the more undifferentiated cells (Redman).

### Clinical Evolution

#### Tumors Arising From the Cortex —

*Adenomas*—The overwhelming majority of adenomas of the cortex do not produce clinical symptoms and are only found at autopsy. A small group of these tumors, however, are characterized by their variable hormonal changes which, according to Cahill (1941), may be subdivided as follows

- 1 Changes in the female toward masculinity (androgenic)
- 2 Changes in the immature male toward maturity (androgenic)
- 3 Changes in the male toward femininity (estrogenic)
- 4 Sexual changes combined with other metabolic changes
- 5 Metabolic alterations in the blood, etc. psychic and emotional changes but no changes in the secondary sexual characteristics (Cushing's syndrome)

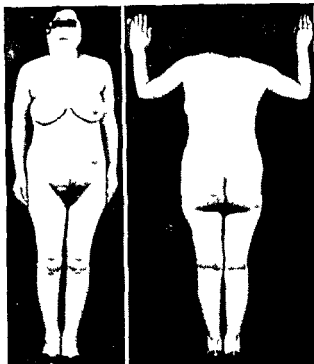


Fig. 49.—Patient 27 years of age presenting a Cushing's syndrome due to an adenoma of the suprarenal cortex. (From Cahill G. F. Surg. Gynec. & Obst. 1941.)

The most common among these hormonal changes is the tendency of females to undergo virilizing alterations. These changes usually occur after puberty and before the menopause. Amenorrhea is often noted; the body becomes masculine, the hair distribution acquires the characteristics of the male (Fig 541), and the voice may change. Young males show a precocious tendency toward maturity with premature sex and muscular development but usually without development of female characteristics. Rarely a feminizing tendency may be observed in the male with changes in body type, enlargement of breasts, increased pigmentation of the nipples, and diminution in size of the testicles (Levy Simpson). The hormonal changes produced by adenomas of the suprarenal

the enlargement of the subcutaneous lymph nodes may be noticeable only in the later stages of the disease even during periods of atrophy.

*Mixed Types.*—The course of evolution of the mixed type of tumor does not differ from that of the neuroblastoma.

### Diagnosis

Unfortunately, the diagnosis of a malignant tumor of the suprarenal gland is often made because of the presence of alarming general symptoms rather than for symptoms produced by the tumor in its local development. Benign tumors, too, may offer difficult local diagnosis. In children the presence of an enlargement of the lymph nodes, cryptorchidism and proper cervical adenopathy is an important clue to the diagnosis, but the diagnosis is more difficult when the tumor takes on a terminal form of development with enlargement of the lymphoid subcutaneous nodes. An exploration biopsy or an exploratory laparotomy may be necessary in such cases for diagnosis.

In patients having paroxysmal attacks such as those produced by pheochromocytoma the attacks should be carefully observed if possible with a constant recording of the blood pressure. An intravenous injection of 0.05 mg. of histamine may produce typical paroxysms and be given in order to facilitate the diagnosis. Rarely. In tumors producing feminizing changes attention should be given to the redistribution of the body configuration, external genitalia, breasts, and gonads.

**Röntgenologic Examination.**—When a tumor of the suprarenal gland is suspected a roentgenologic examination of the abdomen is indicated. The tumor may be demonstrated by a simple abdominal roentgenogram but an intravenous pyelogram or sometimes a retrograde pyelogram may help in revealing displacement and pressure on the kidney. Tomography may be helpful in determining the presence of small tumors (deVries). Roentgenograms taken after insufflation of air in the region of the adrenal (Fig. 544) are particularly useful to demonstrate relatively small tumors or to rule out the suprarenal gland as a possible primary site of disease. Cope and Cavill (1941) reported 400 such insufflations without untoward complications. This procedure however is not indicated when a vesicular tumor such as neuroblastoma is suspected for in such instances the chances of air emboli due to dilated numerous blood vessels are high.

For a suspected neuroblastoma skeletal films should be taken. Metastases are usually generalized and in practically all bones proximal to the knee and elbow joints. If the long bones show bilateral symmetrical involvement a neuroblastoma is probably present (Wright). These changes will be present particularly in the diaphyseal portions of the humerus and distal portions of the femur. Although they are usually osteolytic, they are not infrequently mixed in type. The bones of the pelvis and skull may show extensive replacement. It is not rare for the metastases of a neuroblastoma to mimic the roentgenologic changes in Ewing's sarcoma with elevation of the periosteum in the upper ends of long bones and with production of bone spicules at right angles to it (Fig. 545). The skull very frequently shows a characteristic osteolytic involvement.

clinical types of evolution of neuroblastomas of the suprarenal gland. These do not correspond to any pathologic differences but are merely variations in the clinical findings and course. The Pepper type is characterized by a distention of the abdomen from enlargement of the liver, mesenteric lymph node metastases, rapid loss of weight and strength, and anemia. The tumor here is found in the right suprarenal gland, which explains the rapid involvement of the liver. Metastases to the bones of the skull are seldom observed, but the mesenteric nodes are always considerably enlarged. The Hutchison type is characterized by the peculiar onset of ecchymosis of the eyelids, proptosis of the eye and enlargement of the preauricular, submaxillary, and upper cervical



Fig. 543.—Baby 18 months of age presenting a typical Hutchison's syndrome due to a neuroblastoma of the right suprarenal gland. Note ecchymosis, slight exophthalmos and enlargement of the right submaxillary and buccal lymph nodes.

lymph nodes on the same side (Fig. 543). These symptoms are caused by metastases in the bones of the skull which have an unexplained predilection for the region of the orbit. Neuroblastomas which produce this clinical picture may be found in the left or right suprarenal gland. It has been mistakenly thought that the Hutchison syndrome was produced by tumors arising in the left suprarenal gland just as the Pepper syndrome was produced by those arising on the right side. Of the ten cases reported by Hutchison in his original publication, only 6 arose from the left suprarenal gland. Frew observed that when the tumor was on the right side, the metastasis to the orbit, the exophthalmus, and ecchymosis also occurred on the right, and when the tumor was on the left, these changes developed first on the left orbit. The size of the primary tumor and



reported on a patient with carcinoma of the suprarenal cortex with feminization and markedly increased estroge excretion in whom the symptoms and increased estrogen excretion disappeared following operation but recurred later due to recurrence

Examination of the blood may demonstrate the presence of pressor substances with a pheochromocytoma. During an attack, the blood sugar may also become elevated. Assay of the tumor for pressor substances is often diagnostic (Beers)



Fig 545—Roentgenogram of the distal portion of the femur in a case of neuroblastoma of the suprarenal gland showing osteolytic changes with separation of the periosteum and areas of bone formation

**Biopsy**—When a specimen is obtained for pathologic examination in a case of generalized neuroblastoma, the typical rosettes in the primary tumor may be absent in the secondary implants, and consequently there may be a difficulty in differential diagnosis with Ewing's tumor or, more often, with lympho-

multiple areas of destruction (Doub). In tumors of the cortex which give the clinical syndrome suggesting pituitary basophilism, roentgenograms of the skull are indicated. Generalized osteoporosis may also be present.

**Laboratory Examination**—In patients suspected of having a tumor of the suprarenal cortex a study of the androgen (17 ketosteroids) and estrogen excretion may be useful. The androgens in the urine are usually elevated in both adrenal cortical tumors and in simple adrenal cortical hyperplasia. However, Talbot pointed out that with tumors of the suprarenal cortex the beta alcoholic and nonalcoholic fraction of the 17 ketosteroids is usually prominently elevated, while the output is normal or only slightly elevated in patients with cortical hyperplasia. Further evidence of the value of the study of the androgen excretion was shown by Crooke who investigated four patients with Cushing's syndrome. He reported two who presented an increased androgen excretion and



Fig. 544—Roentgenogram of the abdomen after air insufflation in the region of the suprarenal glands showing a voluminous suprarenal tumor on the left. (From Cahill G. F. Surg. Gynec. & Obst. 194.)

both of these had a tumor of the suprarenal cortex, while the other two with normal androgen excretion had a basophile adenoma of the pituitary. In four patients with cortical carcinomas of the adrenal, Frank reported increased amounts of estrogenic substance in the urine as high as 1,000 to 10,000 mouse units per liter with a negative pregnancy test. He reported negative results for estrogenic substance in other conditions such as cortical adenoma, suprarenal hyperplasia, and syndromes suggesting basophilism. This problem is further complicated by the fact that a few patients excrete excessive quantities of both androgens and estrogens, and unfortunately some patients with adrenal cortical tumors have normal values for one or both hormones (Mason). Hormone study, however, may be of value in detecting recurrence of a malignant tumor. Levy Simpson

TABLE XLII DIFFERENTIAL DIAGNOSIS OF NEUROBLASTOMA OF SUPRARENAL GLAND

	AGE	ABDOMINAL MASS	ORBIT	BONE CHANGES	LYMPH GLANDS	LYMPHATIC SYSTEM	RESPONSE TO RADIOTHERAPY
Neuroblastoma	0 to 6 years	Often not felt	Proptosis of eye, ecchymosis of eyelids often present	Osteoplastic and osteolytic changes in long bones and skull common	May reveal extrinsic tumor masses	At times diagnostic	Immediate response
Wilms' tumor	0 to 9 years	Invariably large		Not present	Reveal intrinsic tumor of kidney	Normal	Delayed response
Chloroma (myelogenous leukemia) and acute leukemia	0 to 5 years	Not present but may have enlarged spleen and/or liver	Proptosis of eye, ecchymosis of eyelids may be present	Invariably osteolytic very similar to neuroblastoma	Normal	May be diagnostic, white blood count invariably elevated	Immediate response
Ewing's sarcoma	5 to 25 years	Not present		Almost identical with neuroblastoma	Normal	May resemble neuroblastoma	Delayed response

sarcoma In these instances the pathologist will have to rely on the clinical, radiographic, and laboratory information which is available in order to reach a diagnosis Stout has used tissue culture as a means of identifying neuroblastomas

**Differential Diagnosis**—In tumors of the suprarenal cortex which produce precocious puberty, virilism of the female, or feminization of the male the differential diagnosis concerns pituitary basophile tumors and ovarian arrhenoblastoma The metabolic and sexual disorders produced by pituitary basophile tumors are the most difficult to differentiate, but perhaps the most important differential point is the excretion of 17 ketosteroids which, as indicated by Crooke (1939), is normal in pituitary tumors and increased in tumors of the suprarenal cortex Ovarian arrhenoblastomas are rare and, because of the virilizing signs and symptoms present may be difficult to differentiate from tumors of the suprarenal cortex On pelvic examination, however, they are usually palpated as a large unilateral tumor and they can also naturally be observed at exploratory laparotomy A clinical basis for a differential diagnosis with this condition will be found in Table XLI Precocious puberty may also occur in tumors of the hypothalamus but these lesions are also extremely rare only seventeen having been reported in the medical literature (Weinberger) Tumors of the testis can also cause sexual precocity (Rowland) Obviously the clinical or radiographic demonstration of a tumor mass in the suprarenal region is an important factor in the differential diagnosis with all the conditions mentioned in the foregoing

TABLE XLI DIFFERENT CHARACTER OF SEXUAL ALTERATIONS AND METABOLIC DISORDERS WHICH MAY BE FOUND IN TUMORS OF SUPRARENAL CORTX IN PITUITARY BASOPHILE TUMORS AND OVARIAN ARRHENOBLASTOMA  
(From data by Dorfman Crooke and Goldzieher)

	PITUITARY BASOPHILE TUMORS	TUMORS OF THE ADRENAL CORTX	OVARIAN ARRHENOBLASTOMA
Obesity	Face and trunk (gir- dlelike)	Face and trunk	Not characteristic
Echymosis	Common	Common	Absent
Rubicundity	Usual	Usual	Absent
Hypertension	Common	Usual	Absent
Carbohydrate toler- ance	Low	Low	Normal
Osteoporosis	Common	Common	Absent
Sexual development	Retarded	Precocious	Precocious
Female genital or- gans	Normal or atrophic	Hypertrophy of clitoris	Hypertrophy of clitoris
Hirsutism	Redominant on cheek, silky lanugo hair	Redominant chin up- per lip, and rest of body, coarse dark hair	Generalized masculine distribution
17 ketosteroid excre- tion	Normal	Increased	

The differential diagnosis of benign tumors of the suprarenal medulla is only a problem in the case of pheochromocytomas In these rare medullary tumors, the paroxysmal attacks of hypertension may sometimes last a consider-

The treatment of *benign tumors of the suprarenal medulla* is also surgical excision. In the case of pheochromocytomas it is advisable to administer desoxycorticosterone acetate and an extract of suprarenal cortex with a high salt diet preoperatively. Because control of the blood pressure is vital throughout the operation spinal anesthesia should not be used. During operation intravenous and intramuscular epinephrine should be given. These three drugs may have to be administered following operation depending on symptoms and signs of adrenal insufficiency (Biskind). Rough handling of the tumor at the time of operation should be avoided because of the startling effects with extremely high blood pressure.

A diagnosis of *malignant tumor of the suprarenal medulla* is unfortunately seldom made before extensive metastases or massive involvement of the liver have occurred. In the few instances however in which an early diagnosis is made surgical excision is indicated.

**ROENTGEN THERAPY**—The treatment of benign and malignant tumors of the suprarenal cortex by means of radiation therapy cannot possibly compete with the results of surgical excision. This form of treatment has never been advocated in benign tumors of the medulla. Theoretically there could be doubt as to the possibility of sterilizing neuroblastomas by means of radiations. Its use as a preoperative measure has been discarded because of the time element and its questionable advantage as an adjunctive measure. The experience of radiotherapists with this type of tumor has been very limited. Farber (1946) has reported on four patients with inoperable neuroblastomas with metastases to the liver (pathologically verified) who were living after radiotherapy alone. These results should encourage further trial of this form of treatment.

### Prognosis

The prognosis of *benign tumors of the suprarenal cortex* is very good. In cases where there have been sexual changes a regression of these symptoms may occur after surgical excision of the tumor (Fig. 541) but hirsutism and changes in the voice usually persist.

*Adenocarcinoma of the adrenal cortex* is often bilateral and often is diagnosed after metastases have occurred. However, if the tumor is unilateral and is resected in its earlier stages some cases may be cured.

The prognosis of *benign tumors of the suprarenal medulla* is also very good. The prognosis of *pheochromocytomas* depends entirely upon the appreciation of the physiologic changes which accompany the tumor. The operative mortality and therefore the prognosis will depend on how well pre- and postoperative care is planned.

In the past cases of *neuroblastoma of the suprarenal medulla* have been considered as hopeless. A revision of this conception should be entertained. One patient reported on by Lehman was living and well twenty years after surgical excision. Farber (1940) reported on forty patients ten of whom were alive from three to eight years after surgical treatment. He also reported on four patients (1946) with pathologically proved metastases to the liver who were well follow-

able period of time (Palmer), and the differential diagnosis will have to be established with essential hypertension and hyperthyroidism. The sensation of constricting pain within the chest which sometimes accompanies attacks may lead to the erroneous diagnosis of coronary occlusion, but the clinical history and the electrocardiogram will be of help in establishing the differential diagnosis. Hyperthyroidism may also be confused, but palpation of the thyroid gland, lack of eye signs of hyperthyroidism and estimation of the basal metabolic rate will serve to differentiate it. The increased amount of pressor substance found in the blood at the height of a paroxysmal attack and the disappearance of its effect after administration of ergotamine will further prove the presence of a pheochromocytoma (Hyman).

The differential diagnosis of *malignant tumors of the suprarenal medulla* may have to be established with Wilm's tumor, Ewing's sarcoma, chloroma and generalized lymphosarcoma (Table XLII). In Wilm's tumor of the kidney there is invariably a large abdominal mass and the intravenous pyelogram reveals intrinsic deformity of the kidney in patients in good general condition. The bone changes observed in the radiographic examination of a Ewing's sarcoma are almost identical with those of generalized neuroblastoma, which may be confusing in young children. However, the general condition in patients with Ewing's sarcoma is better and there are no orbital or abdominal signs. Chloroma, a variety of myelogenous leucemia, produces ecchymosis of the eyelids and proptosis of the eye which are comparable to that of the Hutchison type of neuroblastoma. However, in cases of chloroma, no abdominal mass is felt and the peripheral blood count shows an increased number of immature cells of the myeloid series. A bone marrow biopsy will settle the problem of diagnosis.

It is well known that metastases from other primary tumors are frequently found in the suprarenal glands, in fact, in some autopsy series the percentage of metastases to the suprarenal gland is above 25 per cent (Glomset). In spite of this frequent occurrence, there is only rarely a question of differential diagnosis between these metastatic tumors and primary tumors of the suprarenal gland.

### Treatment

**SURGERY**—*In tumors of the suprarenal cortex* surgical excision is the best treatment. An abdominal approach seems to be most logical (Brunschwig). It facilitates a preliminary exploration to ascertain whether the tumor is bilateral. If the tumor is located on the anterior surface of the kidney, then it can be removed without simultaneous nephrectomy. In females with virilizing symptoms, when the diagnosis of suprarenal tumor is questionable, an abdominal approach aids exploration of the ovaries for a possible arrhenoblastoma. Biskind suggests that the exploration of the suprarenal glands be started on the right side because of the greater number of tumors found there. But an exploration of both regions is necessary in every case to ascertain the presence of the opposite suprarenal gland, which may be atrophied or even absent in tumors of the suprarenal cortex (Lukens). Removal of the tumor under these circumstances may result in death. The extirpation of a hyperplastic suprarenal gland mistaken for the primary tumor has resulted disastrously (Volhard).

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ing radiation therapy, but he has seen no patient who has done well after the development of bone metastases. He states that when the patients are well one year after treatment, the chances of recurrence are remote. Very infrequently a neuroblastoma undergoes a spontaneous regression or transition from a very undifferentiated variety to a benign variant of medullary origin such as ganglioneuroma (Cushing). In the advanced cases of neuroblastoma in which generalized bone metastases are present the patient usually only lives a few months, and the younger the patient, the shorter the duration of the disease.

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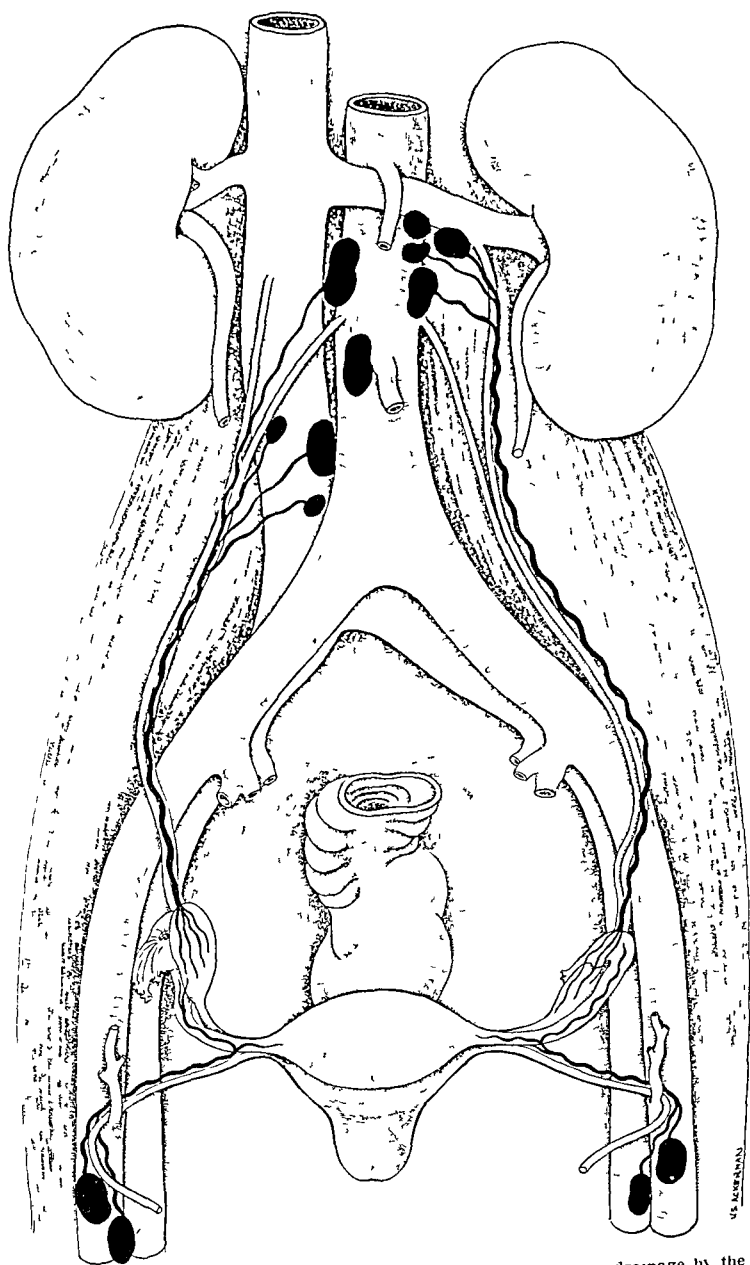


Fig 546—Anatomic sketch of the lymphatics of the ovary showing drainage by the para aortic lymph nodes. On the right the draining nodes extend from the kidney pedicle to the termination of the aorta. There is also an inconstant drainage toward the external iliac nodes.

## Chapter XIV

### CANCER OF THE FEMALE GENITAL ORGANS

#### TUMORS OF THE OVARY

##### Anatomy

The ovaries are situated on each side of the pelvis behind the broad ligament and the Fallopian tubes and 1.5 to 2 cm. in front of the sacrospinous symphysis. They have a somewhat flattened ovoid form and during genital life have a pink color and deep crevices. After the menopause the ovaries have a tendency to become atrophied, sclerotic, and smooth. They are attached to the posterior aspect of the broad ligaments by the meso ovarium (Fig. 586) and to the uterus medially by the utero ovarian ligament but the most important means of fixation is the suspensor ligament, which connects the ovary with the pelvic wall.

The ovaries are supplied with blood by the ovarian artery, which is a branch of the abdominal aorta, and are also abundantly interspersed with nerves.

**Lymphatics**—The lymphatics of the ovary form a rich network that surrounds the Graafian follicles. The collecting trunks follow an upward direction with the utero ovarian vessels, cross the external iliac vessels, reach the level of the lower pole of the kidney where they turn medially, cross in front of the ureter and terminate in the lumboaortic lymph nodes. Normally the intersection with the ureter is found higher on the left than on the right. Also on the left side the lymphatic trunks are more compact and terminate in a closely related group of nodes under the kidney pedicle. On the right side the lymphatics become separated toward the end and diverge to terminate in precaval and laterocaval nodes which may be found from the kidney pedicle down to the termination of the aorta (Rouviere). In addition another collecting trunk has been described (Marcille) which is not constant (Fig. 546). This trunk follows a lateral direction in the broad ligaments to terminate in the nodes of the external iliac chain.

##### Incidence

Ovarian carcinomas make up about 15 per cent of all pelvic cancers. There is about one carcinoma for every three or four ovarian tumors. Lynch found 110 of 302 tumors of the ovary. Naturally, lesions which are not true tumors (such as various types of functional cysts) should not be included. The relative proportion of benign and malignant tumors is undoubtedly influenced by the individual pathologic interpretations of what is a benign and what is a malignant tumor.

##### Pathology

**Gross and Microscopic Pathology**—A knowledge of the embryology of the ovary is necessary in an understanding of the development of ovarian tumors.

possessing no endocrine function. This tumor may also occur in gonads which have differentiated into ovaries or testes. The first evidence of sex differentiation is seen in the development of the so-called sex cords or medullary tubules which converge toward the hilum of the gland. In the gonad destined to develop as testes, these cords become canalized and later constitute the seminiferous tubules. When the gonad is to become an ovary, the same preliminary sex cord differentiation is noted, but this soon regresses and ovarian differentiation proceeds over this earlier "testicular" scaffolding. Certain cells of the preliminary testicular phase with male-directed potentialities may persist in the medulla of the ovary and may be the source of the development of arrhenoblastomas (Meyer). The regression of sex cords is followed, with overlapping, by a second wave of differentiation with the formation of cell columns which are definitely female.

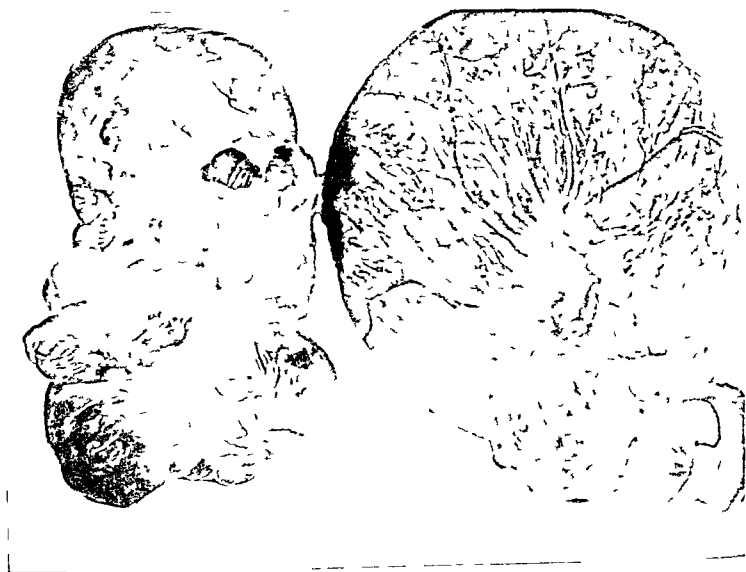
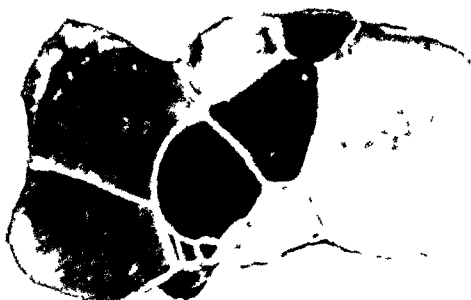


Fig. 549—Bilateral moderate-sized benign serous cystadenoma of the ovaries

The ovarian mesenchyme is probably the parent tissue of both granulosa and theca cells, which is a point of importance in the understanding of the feminizing group of tumors (thecoma and granulosa-cell tumors). Further differentiation of the follicular apparatus is accompanied by grouping of epithelial cells about the germ cells with the formation of primitive follicles. In this process small clumps of redundant granulosa cells are sometimes left and may at times be observed in the ovaries of children and even less frequently in those of adults. Meyer looks upon these as the origin of granulosa-cell growths, but Novak believes that they are more likely to be traced to the parent ovarian mesenchyme.

A classification of ovarian tumors is essential for understanding the clinical evolution, pathology, treatment, and prognosis (Table XLIII)

[illegible]

characteristic loculations (Fig 548) and papillary burgeoning outgrowths which are usually seen growing within the wall of the cyst (Fig 547), on its surface, or on the peritoneum. When the pseudomucinous tumor grows in the peritoneum (Fig 553), it forms large masses of gelatinous tumor resembling frog spawn. The fluid of the serous tumor has the characteristics of a transudate, while that of the pseudomucinous variety has a viscid, slimy quality. Both of these cystic tumors are moderate in size and freely movable and lie mostly outside of the pelvis. Torsion of the pedicle occurs more frequently in the benign than in the malignant tumors of the ovary because the malignant variety quickly becomes fixed.



Fig 550 —Photomicrograph of a fibrous type of serous cystadenoma of the ovary which is in variably benign (low-power enlargement)

Microscopically there are many variants of the serous cystadenoma. Taylor not only emphasized this extreme variation, but also pointed out that the interpretation of these tumors is extremely important and is, in fact, the key factor in obtaining statistics of cure for ovarian carcinoma. The predominantly fibrous serous cystadenoma with very little epithelial element is invariably benign (Fig 550). This tumor tends to become more cellular, and since the acini show layering of the cells, it may be difficult to determine whether it is benign or malignant (Fig 551). Individual tumors may behave in an unpredictable manner. Cilia are often seen in the serous variety, and psammoma bodies are plentiful in the more differentiated forms. This tumor is very frequently bilateral, but whether it arises spontaneously in both ovaries or metastasizes from one to the other is hard to determine. Certainly, in the unilateral malignant serous tumors, it would be of value to section the opposite ovary, particularly the hilar region, for evidence of lymphatic metastases.

TABLE XLIII COMPARATIVE DATA ON OVARIAN TUMORS

ORIGIN	TYPE OF TUMOR	% OF ALL BENIGN	% OF ALL MALIGNANT	% BILATERAL
Germinal epithelium	Serous cystadenoma—benign (50%)	30	70	50
	Serous cystadenocarcinoma—malignant (50%)			50
Germinal epithelium	Pseudomucinous cystadenoma (90%)	40	13	5
	Pseudomucinous cystadenocarcinoma (5%)			
Misplaced blastomeres	Cystic teratoma (97%)	10		12
	Struma ovarii		1	
	Carcinoma (usually squamous) (3%)			
Sexually indifferent cell inclusions (Walthard)	Brenner tumor (invariably benign)	1	0	0
Ovarian stroma	Fibroma (invariably benign)	5	0	10
Mesenchyme	Thecoma (invariably benign)	5	0	0
Undifferentiated embryonic cells of genital ridge	Dysgerminoma (often malignant)		1	0
Mesenchyme	Granulosa cell tumor—benign (60%)	1	10	5
	Granulosa cell tumor—malignant (40%)			
Embryonic remnants male directed cells in the region of rete ovarii	Arrhenoblastoma—benign (80%)	less than 1	less than 1	0
	Arrhenoblastoma—malignant (20%)			
Undetermined	Carcinoma undifferentiated		0.10	0.0
Mesenchyme	Sarcoma			0
Metastases from stomach, bowel, gall bladder, etc.	Krukenberg tumor			100

*Serous and Pseudomucinous Tumors*.—To some extent these two types of tumors are similar and it is important to know the distinguishing gross characteristics. The serous tumor is frequently bilateral and, because of this may be identified from the pseudomucinous which is most frequently unilateral. This differentiation has practical significance when a decision must be made regarding the removal of one or both ovaries (Table XLIV). The serous variety presents

TABLE XLIV DIFFERENTIAL CHARACTERISTICS OF SEROUS AND PSEUDOMUCINOUS TUMORS OF OVARY

	SEROUS	PSEUDOMUCINOUS
Frequency	Benign varieties about equal in frequency, malignant types predominantly serous	
Bilateral	50%	5%
Size	Moderate	Often huge
Character of fluid	Transudate	Slimy, viscid
Malignant	High percentage	Low percentage
Tendency to metastasize to regional and distant lymph nodes in malignant variant	High percentage	Low percentage
Tendency to implant	High percentage	Relatively frequent
Microscopic characteristics	High columnar, basally situated nucleus	Cuboidal
Cilia	Often present	Never present
Intramammary bodies	Frequent in well differentiated types	Never present

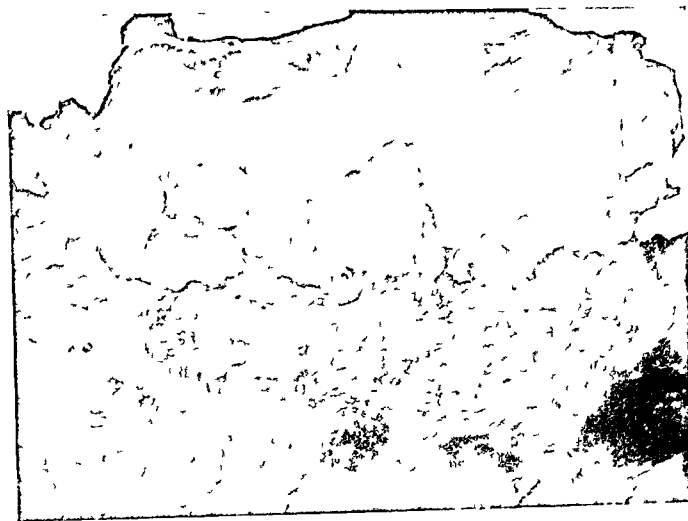


Fig. 553 — Typical implants on the peritoneal surface from a pseudomucinous tumor of the ovary

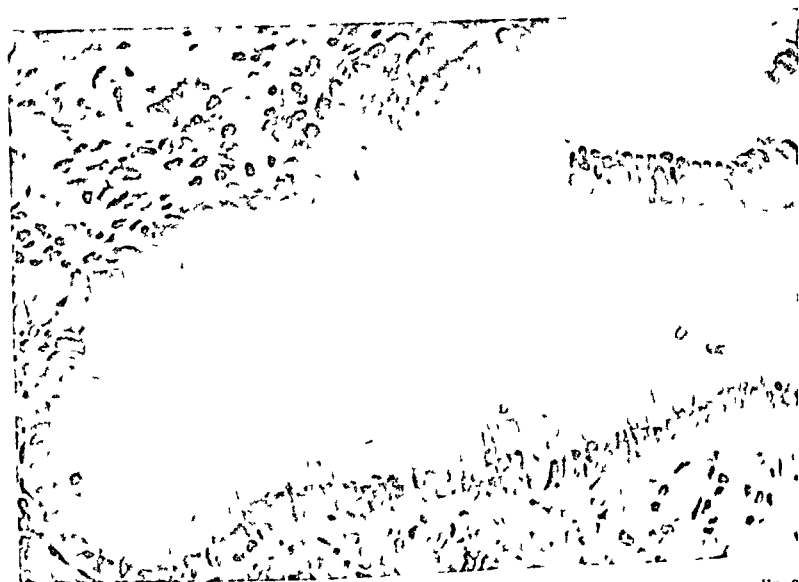


Fig. 554 — Benign pseudomucinous cystadenoma of the ovary with tall columnar cells and basally situated nuclei (moderate enlargement)

The pseudomucinous tumor shows very tall, single layer columnar cells with clear cytoplasm and basally situated nuclei (Fig 554). When it becomes malignant, the cells undergo stratification, there is variation in nuclear size and shape with many mitotic figures, and the tumor tends to invade the wall of the cyst. It does not form psammoma bodies or have cilia. Both serous and

Fig 551



Fig 552

Fig 551—Intermediate type of serous cystic tumor of the ovary which may behave in a benign or malignant fashion (moderate enlargement)  
 Fig 552—Serous cystadenocarcinoma of the ovary obviously malignant (moderate enlargement)



## PLATE VII

Leiomyosarcoma arising from an intraligamentous leiomyoma which was thought to be a carcinoma of the ovary

Large thecoma of the ovary with cystic changes and characteristic small yellow areas

Bilateral serous cystadenocarcinomas of the ovary with tumor growing on the surface of the largest cyst

Granulosa cell tumor with hemorrhage and yellowish zones. The myometrium shows hypertrophy. There was hyperplasia of the endometrium

Bilateral undifferentiated carcinomas of the ovary

Metastatic mucinous carcinoma in the ovary from a primary tumor of the rectum

pseudomucinous neoplasms may present areas of necrosis hemorrhage, infarction or torsion because of an excessively rapid growth

*Cystic Teratoma*—The cystic teratoma is sometimes designated as a dermoid cyst but is more logically called a teratoma because it so frequently contains elements from all three embryologic layers. It has a smooth, shiny surface and it does not, as a rule, attain a large size (average, 8 cm). Before surgical removal the contents are fluid but after removal the cyst wall becomes wrinkled and dry and the contents semisolid. On section the cysts characteristically contain yellow, greasy material in which teeth may be found (Fig 555). Hair is

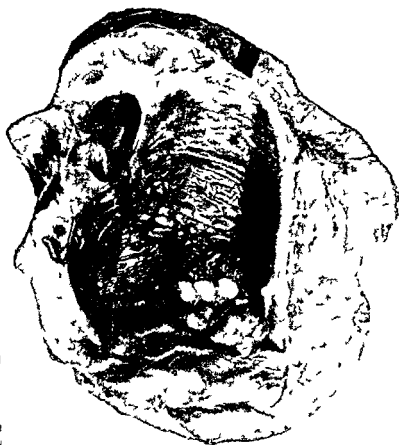


Fig 555.—Cut section of an ovarian teratoma, showing three teeth attached to a rudimentary mandible. (Specimen contributed by Dr. Robert A. Moore, Department of Pathology, Washington University School of Medicine, St. Louis, Mo.)

often present and may be of several colors in the same cyst. There is usually a white shiny unilocular protuberance in one part of the cyst. About 12 per cent of these tumors are bilateral. Rarely they become malignant. 3 of 225 reported by Blackwell contained carcinoma. The solid type is usually malignant.

Teratomas probably arise from misplaced blastomeres, but they may represent a parthenogenetic development of the ovum. Microscopically they are lined throughout by stratified epithelium (resembling that of the skin) which very commonly contains sebaceous glands from which much of the greasy material emanates. Other skin appendages are commonly present (Fig 556).





PLATE VII.

All types of tissue can be found within a teratoma in a large series of cases reported by Blackwell, 100 per cent contained elements of ectoderm, 93 per cent, mesoderm, and 71 per cent, endoderm. Struma ovarii or thyroid tissue was present in 3 per cent of 297 teratomas reported by Gusberg (Fig 557). Plaut studied three struma ovarii biologically and proved that they represented true functioning thyroid tissue. Struma ovarii may show the changes found in a nodular goiter, hyperplasia, or carcinoma (Emge). Teratomas may show an overgrowth of one element and become carcinoma, which is most frequently squamous in nature, but many types of malignant tumors arising from other elements have been reported.



Fig 558—Photomicrograph of a Brenner tumor of the ovary with typical well delineated collection of epithelial cells (moderate enlargement)

**Fibroma**—Fibromas of the ovary are usually firm, grayish-white in color, and cystic, calcification rarely occurs. The average size is 6 cm (Dockerly). In 90 per cent of the cases the tumor is unilateral. Fibromas probably arise from the ovarian stroma. They are made up of connective tissue which has a variable cellular quality, and intercellular edema is common. In Dockerly's 312 cases, ascites was present in fifty-one and hydrothorax in two. The mechanism of the hydrothorax in an ovarian fibroma as well as in the thecoma has been discussed at length. The fluid probably reaches the pleural cavity via the



Fig 556 —Photomicrograph of a teratoma of the ovary showing the lining squamous epithelium, hair follicles, and innumerable sebaceous glands (low power enlargement)

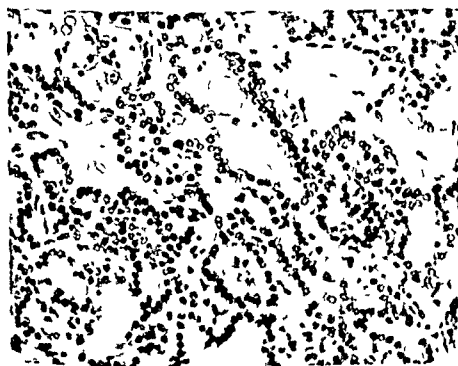


Fig 557 —Photomicrograph of a teratoma of the ovary showing the lining squamous epithelium, hair follicles, and innumerable sebaceous glands (high power enlargement)

and somewhat bosselated, and there is a resemblance to cerebral convolutions, they are soft and have a thin, smooth capsule. On section they are cellular and gray, and areas of hemorrhage and necrosis are common. Dysgerminomas probably arise from undifferentiated embryonic cells of the genital ridge (Meyer). The individual cells are large with big nuclei, clear cytoplasm, and rather prominent nucleoli. At times a tuberculoid reaction of the stroma occurs and epithelioid and giant cells are seen, but this reaction is undoubtedly inflammatory and nonspecific (Heller). Lymphoid infiltration of the stroma is prominent (Fig. 559). It is difficult to differentiate the benign from the malignant tumor, but probably a greater number of these tumors are malignant than have been cited. Their histologic appearance and behavior are somewhat similar to the seminoma. They do tend to recur, however, and it is probable that their malignancy is often underestimated because of short follow-up.



Fig. 560—Photomicrograph of a thecoma of the ovary with hyaline-like plaques and typical arrangement of cells (moderate enlargement).

*Granulosa-Cell and Theca-Cell Tumors*—These two tumors are discussed together because they have a common ancestry and because an increasing number of cases are being reported in which elements of both are found in the same tumor. Further evidence of such an association is substantiated by experimental work. The production of granulosa-cell and theca-cell tumors in mice following irradiation (Furth) gives further support to Fischel's theory that the ovarian parenchyma is a result of the differentiation of the mesenchymal cell mass. Furth demonstrated in mice that these tumors arise from mesenchyme rather than from derivatives of coelomic epithelium. If the tumor develops predominantly along epithelial lines, it becomes a granulosa-cell tumor, if it assumes predominantly connective tissue elements, it develops into

lymphatics for it has been demonstrated that there are lymphatic vessels connecting the diaphragmatic peritoneum with subpleural lymph channels (Rubin)

**Brenner Tumor**—This tumor, invariably unilateral and benign, may be very small or may grow slowly to weigh 15 pounds. It is fairly firm and on cut section suggests a fibroma except for the yellowish tint to its surface. Games (1936) observed small cavities (0.1 to 2 cm.) containing opaque, viscid, yellow brown fluid. At times this tumor is solid and is situated in the wall of a cyst (usually pseudomucinous).



Fig 559—Photomicrograph of a dysgerminoma of the ovary. Note uniformity of cells and infiltration of lymphocytes (moderate enlargement)

Meyer believes that Brenner tumors arise from the sexually indifferent cell inclusions described by Walthard. The tumor is composed of abundant connective tissue with islands of compact polyhedral epithelial cells which have a characteristic longitudinal grooving or folding of their nuclei (Arey), presenting no mitoses (Fig 558). Novak (1939) emphasized that this combination of epithelial cells and connective tissue framework must be present before a diagnosis of Brenner tumor can be made. There is some tendency to cystic degeneration of the epithelial nests, and the cells may take on a columnar appearance with a mucoid secretion, Novak (1939) and Meyer believe a certain but probably small proportion of pseudomucinous cysts may therefore have their origin in the Brenner tumor. Brenner tumors contain no fat but do contain glycogen and at times mucin. This is of differential value when granulosa cell tumors are considered for the latter contain fat and no glycogen (Lox).

**Dysgerminoma**—These tumors are often large, bilateral (about 25 per cent), and apparently more common in the right ovary. Their surface is smooth



nant type varies from 20 to 60 per cent. The higher estimates are probably more nearly accurate, for these tumors tend to recur many years after surgical treatment. Naturally, if the tumor has spread beyond its capsule, it is malignant. This consideration is probably more important in determining its malignancy than the cytology.

Reticulum stains are helpful in differentiating theca-cell and granulosa-cell tumors. The theca cells are surrounded by reticulum, while granulosa and lutein cells are not enclosed at all (Triauf). Special fat stains according to the technique of Hoen-Romeis reveal different types of fat. Triauf states that the hormone activity of these tumors is somewhat parallel to the phospholipid and free cholesterol content.



Fig. 562.—Photomicrograph of an ovarian arrhenoblastoma. Note resemblance of the large collection of cells to interstitial cells (Courtesy of Dr. John Hobbs, Department of Gynecology and Obstetrics, Washington University School of Medicine, St. Louis, Mo.)

Both the granulosa-cell and theca-cell tumors are associated with hyperestrogenism and myohypertrophy of the uterus, and endometrial hyperplasia is a frequent concomitant finding. Endometrial carcinoma has also been reported in conjunction with both of these tumors. Henderson reported that five of twenty-one granulosa-cell neoplasms were associated with carcinoma of the endometrium. Three of twenty-three thecomas of the ovary reviewed by Banner had also adenocarcinoma of the endometrium. Triauf (1937) believed that even if the amount of estrogenic hormone secreted by theca-cell tumors were small, its effect on the endometrium and breast would be maximum because of its unopposed action (absence of corpora lutea and presumably of progesterone). It should be stressed that the hyperplasia of the endometrium associated with these tumors is extremely difficult to differentiate from adenocarcinoma and it

The gross characteristics of these two tumors are considerably different. The thecomas are invariably benign and unilateral and do not reach a large size usually measuring between 5 and 10 centimeters. They are firm, and on cut section the most important point in their differentiation from fibromas is the presence of small yellowish areas averaging 2 mm (Plate VII). The larger tumors tend to be edematous and cystic. Ascites was present in seven of twenty-three cases reported by Rubin. The microscopic examination reveals large amounts of connective tissue with small abundant hyaline plaques (Fig 560), and if the tumor is stained by fat with sudan III, large amounts of intracellular, sudanophilic material are observed. Differential staining for various fractions has been shown by Wolfe to be of value. This fat represents an increase in cholesterol and cholesterol esters.



Fig 561—Photomicrograph of a granulosa cell tumor of the ovary with pseudosolitary arrangement and uniformity of cells without mitoses (moderate enlargement)

The granulosa cell tumor is a common ovarian neoplasm. It is usually classified with malignant or solid ovarian tumors and it is estimated that it makes up at least 10 per cent of this group. Usually it is of moderate size, but very large granulosa cell tumors have been described. It is practically never bilateral. On section it is cellular and areas of hemorrhage and necrosis are frequent (Plate VII). Luteinization is not infrequent and gives the tumor a yellowish cast. Microscopically, a granulosa cell tumor may have a folliculoid, cylindroid, or sarcomatoid appearance (Fig 561). All these variants can coexist in the same tumor in different areas. Individual cells infrequently show mitotic figures. It is extremely difficult microscopically to say which tumor is benign and which is malignant, the reported proportion of tumors of the malig-

Some of the tumors designated as cystic are probably primarily solid, and secondary degenerative phenomena have caused cyst formation.

*Rare Tumors*—Chorioepitheliomas arising within a teratoma have been reported. Primary melanocarcinomas possibly arising from teratomas, and other rare tumors such as hemangiomas, lymphangiomas, leiomyomas, have also been reported in the literature.



Fig. 563—Bilateral metastatic carcinoma in the ovaries (Krukenberg tumor) from a primary lesion in the stomach. (Specimen contributed by Dr. Robert A. Moore, Department of Pathology, Washington University School of Medicine, St. Louis, Mo.)

**MURINE SPREAD**—The serous and pseudomucinous cystadenocarcinomas tend to grow through the wall of the cyst and implant on the peritoneal surface. The implants of the serous type are easily recognized as small, cauliflower-like nodules often in close proximity to the primary tumor. These nodules have been known to regress spontaneously after removal of the primary tumor. Pseudomyxomata peritonei result in the implantation of innumerable gelatinous nodules on the surface of the peritoneum. The malignant serous tumor tends to metastasize to nodes along the aorta, and it is not too rare for mediastinal and supraclavicular node involvement to occur, followed later by metastases to the lungs and liver. The pseudomucinous cystadenocarcinoma most commonly spreads by implantation and local invasion within the peritoneal cavity and is reluctant to metastasize distantly.

is probable that some of the cases reported as carcinoma were merely bizarre hyperplasias. Fibroadenomas (McCarty) and even mammary carcinoma (Finkler) have also been concurrently reported.

**Arrhenoblastomas**—These tumors are invariably unilateral, solid, and often hemorrhagic. Their color varies between yellow and reddish blue, and multicentric nodules are usually present.

Meyer and Novak believe that arrhenoblastomas arise from embryonic remnants of the seminiferous tubules in the region of the hilus of the ovary. Bell believes that the degree of masculinization in arrhenoblastoma is dependent upon the prominence of pale interstitial cells. Microscopically one tumor can show all gradations from normal testis to abortive attempts at tubular formation of sarcoma-like tumor (Fig. 562). Spielman demonstrated the presence of lipid droplets within the cytoplasm of both the large polygonal and the fusiform cells. Except in the well differentiated type, spermatogenesis has not been observed (Novak, 1942). Arrhenoblastomas can be divided into three types (Meyer): first the adenoma tubulare testiculare made up of tubules lined by large orderly polygonal cells, second, a typical and atypical tubular form with solid cords or anastomosing strands, and third, the solid form which may resemble a sarcoma but which, with careful study, is found to have cells containing lipid suggesting interstitial cells or imperfect tubules. In the first group, which is the least common, masculinization or defeminization does not usually take place. The third group is most often associated with prominent hormonal alterations.

**Krukenberg Tumor**—The Krukenberg tumors are metastatic neoplasms from primary lesions in the gastrointestinal tract and, in particular, from carcinomas of the stomach (Fig. 563). It is very doubtful if they are ever primary ovarian tumors. They are invariably bilateral, medium in size, and quite firm. The shape of the ovary is preserved. On section small, mucomatous areas are often observed. Microscopically the stroma is usually quite pronounced and a mucous producing carcinoma is present with numerous signet ring cells.

**Sarcomas**—Sarcomas make up a very small group of ovarian tumors. In the past many of them were confused with other ovarian epithelial neoplasms which had sarcomatous like areas. They are bilateral in about 30 per cent of instances and the greater proportion of them are fibrosarcomas. They can arise from fibromas and probably a few from teratomas.

**Carcinomas Unclassified**—An unclassified group of carcinomas is invariably found in textbooks on ovarian tumors. The more careful the study, however, the fewer the number of tumors designated simply as carcinoma. Some of these lesions are probably dysgerminomas, arrhenoblastomas, and granulosa cell tumors and undoubtedly a great many of them arise from previously existing serous cystadenomas. Various subdivisions have been given such as medullary, dyscolar, and carcinoma simplex but these divisions are artificial for practically all of them are very undifferentiated carcinomas tending to form acini. They are bilateral in about one half of the instances and most of them are solid.

about the chin and loss of much of the hair of the scalp. The voice deepens because of lengthening of the vocal cords with increased growth of the laryngeal cartilages. The menstrual cycle is altered, showing first menorrhagia and then amenorrhea. No changes take place in the libido, but sterility is common. The chief complaints, however, are an abdominal mass, amenorrhea, or endocrine alterations.

The Krukenberg tumors may arise like other ovarian tumors and often give no symptoms suggestive of a primary lesion in the gastrointestinal tract. Ascites is frequently present.

The end stages of ovarian carcinomas are usually quite similar. Many of them develop peritoneal implants with increasing ascites and progressive weight loss with death usually brought about by some cause such as bronchopneumonia. Peritonitis commonly occurs in the pseudomucinous group in which pseudo-myxomata peritonii develops. After the masses become very bulky, invasion of the bladder or large bowel may occur. These changes result in death from infection or intestinal obstruction. The serous cystadenocarcinoma and the undifferentiated carcinomas often metastasize distantly, particularly to mediastinal lymph nodes, the evolution being quite rapid due to widespread dissemination. The granulosa cell carcinomas and dysgerminomas as a rule have a slow evolution, but death is still caused by generalized dissemination.

### Diagnosis

**Clinical Examination**—Most ovarian tumors give symptoms which recommend a thorough abdominal and pelvic examination. Large masses are easily palpated in the lower abdomen, ascites (particularly in thecomas and fibromas) and metastatic masses in the omentum are also easily noticed. A bimanual pelvic examination may reveal the presence of a unilateral or bilateral unsuspected ovarian tumor. The examination requires considerable relaxation on the part of the patient and consequently is better done under spinal anesthesia. Tumor implants in the peritoneal cul-de-sac may be felt by rectal palpation. The ovarian tumors can usually be differentiated from other pelvic masses in that they can usually be mobilized, but large tumors which become adherent to the wall may appear as metastatic pelvic masses. When torsion of the pedicle of a cyst has occurred, palpation is painful.

There are certain specific signs and symptoms which may identify various ovarian tumors. The cystic teratomas arise before the cessation of ovarian activity. If found after the menopause, they usually have a long previous history. Approximately 85 per cent of them occur in patients 16 to 55 years old. The cystic teratomas are probably the commonest ovarian tumors prior to puberty and seldom become malignant before the patient is 40 years of age. They are somewhat more common in Negroes. The cystic teratoma, although not usually attached to other organs, may become attached by inflammatory processes, and hair may be extruded through the rectum, bladder, or vagina. Struma ovarii arising in a cystic teratoma may give signs of hyperthyroidism.

The ovarian fibroma occurs most commonly in the fourth, fifth, and sixth decades and practically never occurs before puberty. Meigs has emphasized

The carcinomas which arise from cystic teratomas metastasize widely. The rare thyroid carcinomas coming from struma ovarii may behave like a true thyroid carcinoma and metastasize predominantly to bone. The dysgerminoma and granulosa cell tumors are much slower to metastasize, either to regional nodes or distantly. The Brenner tumor, the fibroma, and the thecoma are invariably benign. The sarcoma may metastasize widely.

### Clinical Evolution

In general, ovarian tumors grow insidiously and can reach a huge size before causing enough symptoms to bring the patient to the physician. Because of this, over one half of the ovarian carcinomas are inoperable when first seen. There are general symptoms and signs which are common to all ovarian tumors. A medium sized tumor may cause abdominal discomfort accompanied by moderate low abdominal pain. As the tumor increases in size, however, pressure symptoms occur which result in dysuria, from pressure on the bladder, constipation from pressure on the rectum, and swelling of the abdomen. With still further increase in size, particularly in the pseudomucinous tumor where the cyst may reach an extremely large size, other pressure symptoms appear which may result in gastric symptoms due to displacement of the stomach or even dyspnea due to elevation of the diaphragm.

Torsion of the tumor often results in an acute abdominal condition. There is severe pain, fever, a tender mass and leucocytosis.

When a nonfunctioning tumor of the ovary becomes carcinoma, ascites and nodular masses in the abdominal and supraclavicular lymph nodes may appear. The patient may lose a great deal of weight and have other symptoms suggesting a malignant process. It should be emphasized that the presence of ascites is not a definite sign of malignant tumor.

The dysgerminoma, occurring usually under 30 years of age, is a nonfunctioning endocrine tumor. About 200 cases have been reported. Changes in the menstrual cycle and amenorrhea are common, and the breasts, uterus and external genitals are often underdeveloped. Pseudohermaphroditism is fairly common.

The granulosa-cell and theca cell tumors produce the most striking clinical changes. In the prepubertal stage the granulosa cell tumor causes increase in size of the uterus, bleeding simulating menstruation, and secondary sex changes. There is increased growth of the breast and even colostrum secretion. Growth of axillary and pubic hair appears. During the normal menstrual cycle, the changes produced by the increase of estrogen accentuate menstrual bleeding and the size of the breasts. In the postmenopausal period the uterus again undergoes hypertrophy, cyclic bleeding again occurs, the vaginal mucosa becomes smooth and soft, and the breasts enlarge. There is no relation between the size of the tumor and its endocrine function.

The arrhenoblastoma, a rare tumor produces striking alterations only in those lesions which show sarcomatoid changes microscopically. Gradual atrophy of the breasts and enlargement of the clitoris develop first with a loss of feminine configuration. The hair takes on a male distribution with increased growth

**Biopsy**—The opportunity of biopsying an ovarian tumor seldom occurs before abdominal exploration but in certain instances the supraclavicular or inguinal nodes may be biopsied. We biopsied a cervical lymph node which revealed metastatic tumor with a pattern compatible with a primary ovarian carcinoma. Careful pelvic examination then revealed a previously unsuspected tumor. Recurrent tumor in a scar, particularly of the serous variety can be biopsied. Rarely an ovarian carcinoma ulcerates through the rectum and a positive biopsy may be attained by proctoscopic examination. In a few instances a curettage may reveal carcinoma invading the endometrium. At operation biopsy of the peritoneal nodules or lymph node metastases can be carried out.

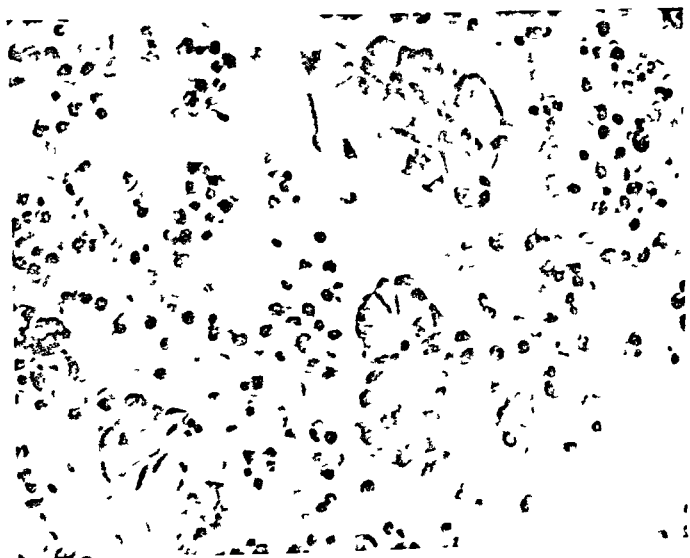


Fig 364—Ascitic fluid sediment from bilateral serous cystadenocarcinomas of the ovary with nests of tumor cells arranged in the form of acini (moderate enlargement)

**Differential Diagnosis**—In many cases the symptoms and signs at first examination are due to a large mass which may be felt abdominally and pelvicly. The most important differential diagnosis is to distinguish an ovarian tumor from a *uterine leiomyoma*. If the leiomyoma is intraligamentous or intimately associated with the uterus, it may be difficult if not impossible, to differentiate it from an ovarian tumor before operation. Because of the characteristic calcification of leiomyomas, the roentgenologic examination may help to differentiate them from an ovarian tumor.

It is sometimes difficult to decide at clinical examination whether the tumor is benign or malignant. It should be remembered that benign tumors such as fibromas, thecomas, pseudomucinous cystadenomas and some rather large serous cystadenomas may produce ascites probably because of mechanical reasons or

that it may be associated with ascites and pleural effusion. Because of hydrothorax, there may be dyspnea, and an erroneous diagnosis of carcinoma of the ovary with metastases to the lungs may be made. Other tumors such as thecomas (Rubin), papillary cystadenocarcinomas (Schenck), pseudomucinous cystadenomas (Millett) may also develop pleural effusion.

The Brenner tumor is a relatively rare tumor, only about 170 cases have been reported (Fox, 1942). They do not occur before 20 years of age, and the majority appear in patients between 30 and 70 years old. Sixty five per cent occur after the menopause and the other 35 per cent between puberty and the climacteric (McGoldrick).

In the estrogen secreting group of tumors which produce signs and symptoms, it may be possible to make a definite clinical diagnosis. Granulosa cell tumors are fairly common and when they occur, particularly in the prepubertal or postmenopausal age, their clinical signs and symptoms are pronounced because of the striking changes engendered. Such changes are not as apparent in patients who are still menstruating. The theca cell tumors, in contrast to the granulosa cell, are rarely observed before 35 years of age and signs of hyperestrogenism, while occurring are not nearly so prominent as in the granulosa cell tumors.

**Roentgenologic Examination**—The roentgenologic examination of the abdomen may reveal a large soft tissue tumor. This examination may be of value in differentiating these tumors from partially calcified leiomyomas. Robins pointed out that cystic teratomas invariably present a rounded or ovoid diminished area of density, banded and mottled in appearance. This area may be limited to the pelvis and is surrounded by a well circumscribed ring of increased density sharply delineating it from the surrounding soft tissue. At times teeth with fragments of a mandible may be observed. In the serous cystadenomas or cystadenocarcinomas, psammoma bodies may be present and characteristically cause multiple fine areas of calcification within the tumor (Loud). A roentgenogram of the chest may reveal an insidious development of metastases. Pleural effusion may be found in thecomas and fibromas but should not be confused with pulmonary metastasis.

**Laboratory Examination**—The examination of ascitic fluid is, at times, very helpful in making a diagnosis of malignant tumor of the ovary (Fig 564). If the ascitic fluid is bloody, the chances are very high that metastatic carcinoma is present. The fluid is spun down and sectioned according to the technique outlined in the chapter on pathology. If ovarian carcinoma is present, the chances of finding it by this technique are high. Acini and papillary masses of cells are frequently observed. The examination of cyst fluid as a method of differentiating ovarian tumors is not practical. Watts has emphasized that fluids differ not only in different types of cysts, but also in different cavities of the same tumor. There is some correlation with secretory activity. Estrogenic hormone in excess amounts in the urine and tumor may be found in granulosa cell tumors (Palmer). The luteinized portion of granulosa cell or theca cell tumors may produce progesterone. Plaut proved that struma ovarii arising in cystic teratomas is biologically, morphologically, and chemically true thyroid tissue.



ploration that the patient has an ovarian tumor, but in a few instances the exact nature is only strongly suspected (such as granulosa-cell tumor or masculinizing arrhenoblastoma). Exploration should determine whether the tumor is unilateral or bilateral, solid or cystic, fixed or movable. Peritoneal implants in the immediate vicinity of the tumor, on the peritoneal surface, and in the cul-de-sac should be searched for. Approximately 80 per cent of ovarian tumors are cystic, and a large proportion of these are benign. The other 20 per cent are solid, and most of these are malignant.

Treatment of the various types of ovarian tumors is often determined on the basis of the gross appearance. The question often arises as to whether to remove one ovary or both ovaries or to do a complete hysterectomy (Table XLV).

TABLE XLV INDICATIONS FOR SURGICAL TREATMENT OF OVARIAN TUMORS (THESE INDICATIONS ARE RELATIVE AND ARE MITIGATED BY THE AGE OF PATIENT, OPERATIVE RISK, PREVIOUS PREGNANCIES, AND OTHER FACTORS)

Fibroma	} Remove one ovary (At times portions can be conserved)
Brenner tumor	
Cystic teratoma	
Thecoma	
Pseudomucinous cystadenoma	Remove entire involved ovary
Solid teratoma	} Hysterectomy, bilateral salpingo oophorectomy
Squamous carcinoma in a teratoma	
Serous cystadenoma apparently unilateral	Remove one ovary or remove both ovaries
Serous cystadenoma bilateral	Remove both ovaries
Serous cystadenocarcinoma apparently unilateral	Remove one ovary or do hysterectomy and bilateral salpingo oophorectomy
Serous cystadenocarcinoma bilateral	Hysterectomy and bilateral salpingo oophorectomy
Carcinoma either unilateral or bilateral	} Hysterectomy and bilateral salpingo oophorectomy
Sarcoma either unilateral or bilateral	
Dysgerminoma	
Arrhenoblastoma	
Granulosa cell tumor questionably benign	Remove tumor or do hysterectomy and bilateral salpingo oophorectomy
Granulosa cell tumor obviously malignant	Hysterectomy and bilateral salpingo oophorectomy

The fibroma is most often unilateral, firm, and not very large and may be accompanied by ascites and even pleural effusion. There are, however, no implants. The Brenner tumor, which is much less frequent, is also most often unilateral, fairly firm, and rarely associated with fluid. The thecoma, generally unilateral, may have the same gross appearance as the fibroma, it is firm and may also be associated with ascites and even pleural effusion. The cystic teratoma, usually unilateral (bilateral in about 15 per cent of the cases), usually has a smooth surface, and its contents will be fluid.

The differentiation of the serous cystadenoma and the pseudomucinous tumor is probably one of the most critical decisions in diagnosis. Pseudomucinous tumors are usually unilateral and very large, while the serous variety is bilateral and of moderate size. The implants present with the serous and pseudomucinous varieties are typical in appearance and easily recognized. If

partially because the tumor itself secretes fluid. The presence of such ascitic fluid does not, therefore, necessarily indicate malignant change.

In the granulosa cell and theca cell tumors the diagnosis can be made if an ovarian mass, feminizing changes, and endometrial hyperplasia are present. In a great many ovarian tumors a definite diagnosis cannot be made until the time of exploratory laparotomy. Some very undifferentiated carcinomas of the ovary may cause cervical or vaginal ulceration. This occurs because of retrograde invasion of the endometrial canal and the patient seeks advice because of vaginal bleeding. Not infrequently these patients have an inguinal adenopathy. It is easy in such cases to be swayed by the appearance and to misdiagnose the case as a carcinoma of the cervix or vagina. Biopsy or curettage shows adenocarcinoma. Carcinoma of the ovary should be suspected if the microscopic examination shows secondary papillary branching and a configuration typical of ovarian carcinoma. There may also be a large mass in the region of the ovary. Carcinoma of the ovary may at times, invade the large bowel and produce symptoms suggesting a large bowel neoplasm but biopsy usually determines the diagnosis. The differential diagnosis of the arrhenoblastoma has to be made with other virilizing tumors. The points of differentiation have been discussed in the chapter on suprarenal tumors. At other times the diagnosis must await exploration.

*Primary carcinoma of the Fallopian tube* is rare, in a series of 10,000 operations for primary malignant disease of the female genital tract performed at the Mayo Clinic between 1910 and 1943, Lofgren found sixteen cases. This tumor occurs most commonly at or near the menopause. In the 192 cases reported by Wechsler 66 per cent occurred between 40 and 55 years of age. Microscopically the tumors are adenocarcinomas and a few are squamous in nature. Extreme epithelial hyperplasia associated with tuberculosis or infection may be present. It may be difficult to tell whether the tumor has originated primarily in the ovary, uterus, or Fallopian tubes because of the spread of the disease. Parsons emphasized that salpingitis and sterility may precede the tumor. The diagnosis is rarely made before operation. Its most common symptom is leucorrhœa, which is often malodorous. Curettage usually shows an atrophic but normal endometrium, for local invasion of the endometrium is rare. Cramping pain in the lower abdomen or pelvis is common but it times may be relieved by a profuse flow of fluid from the vagina. Menorrhagia is very frequent. On pelvic examination a tumor is palpable in the adnexal region in about 80 per cent of the cases and the condition is bilateral in about one third. Metastases spreading to the ovaries, endometrium and inguinal and hypogastric lymph nodes can occur. The distended Fallopian tube may suggest tubo-ovarian inflammatory disease. These tumors should be treated surgically.

Tumors of the tubes are often difficult to differentiate from ovarian tumors, and the diagnosis often is only made at laparotomy.

### Treatment

*Exploration*—An exploratory laparotomy is often necessary for the establishment of a diagnosis. In a high proportion of cases it is known before ex-

ence appears, then roentgentherapy should be administered. Radiotherapy is not indicated for the Krukenberg tumors and is rarely of any value for sarcomas. If a serous cystadenocarcinoma or a pseudomucinous cystadenocarcinoma is not completely removed or is found beyond the ovary at the time of surgery, then postoperative irradiation is mandatory, for there seems to be little doubt that such irradiation prolongs life, gives definite palliation, and, in some instances is a deciding factor in cure. Kerr and Einstein treated a large series of ovarian tumors with postoperative roentgentherapy with good results, they felt that perhaps the papillary cystadenocarcinomas have a somewhat more favorable outlook than the pseudomucinous but that the difference was not significant in view of the small number of cases involved (Kerr). In all of these types of tumors radiotherapy should be given with the idea of sterilizing the neoplasm and thus should be carried with as high dosage as possible.

### Prognosis

It is obvious that the prognosis of the Brenner tumors and the thecomas is excellent after surgical removal. Excision of a fibroma quickly results in the disappearance of any ascitic or pleural fluid.

The cystic teratomas are with a few exceptions benign and therefore their removal almost invariably results in an excellent prognosis. If the tumor is malignant when first seen, it is usually squamous carcinoma, and prognosis is always very poor, even with radical surgery.

The chances of curing a granulosa cell tumor are high if it is encapsulated and removed in its entirety. Even when the tumor has extended beyond the capsule, surgical removal followed by postoperative irradiation gives a good prognosis. It has become increasingly apparent that granulosa cell tumors recur after long periods of time. Jones recently reported three in which recurrence and death took place eighteen, twenty, and twenty-one years after the removal of granulosa-cell tumors.

Florentin reported on five cases of dysgerminoma treated by radiations; four patients survived, two of them for over ten years (Hoche).

The survival statistics of patients with ovarian tumors are exceedingly variable. When all the tumors are considered together, including a large number of granulosa-cell tumors, the over-all five-year survival is deceptively high. The statistics should be dominated by the end results of the serous and pseudomucinous tumors, which normally make up a large proportion of all ovarian neoplasms. The pseudomucinous group, however, are fewer in number than the serous, and their behavior from the standpoint of pathologic examination is more predictable. It is with the serous cystadenoma that the greatest discrepancy arises. Taylor has reiterated and strongly emphasized that the interpretation of these tumors is difficult but that it has considerable influence on reported statistics. It is true that the cases of serous cystadenoma which are predominantly fibrous behave in a benign fashion. It is also true that the very obviously malignant serous cystadenocarcinoma behaves in a malignant fashion. There is, however,

fluid is aspirated from cystic ovarian tumor and it is of the serous type, the fluid will be a transudate, and if it is pseudomucinous in nature it will be viscid and slimy. The dysgerminoma is a rare tumor, often large, unilateral, and rather soft. Its external surface may suggest convolutions of the brain. The Krukenberg tumors, invariably bilateral, retain the shape of the ovary, do not reach a large size, and are quite firm. In a woman under 45 years of age with bilateral ovarian tumors, a careful examination of the gastrointestinal tract particularly stomach, is indicated. At times a unilateral ovarian tumor may be removed in the operating room, sectioned by the pathologist, a frozen section done, and the decision as to further treatment be made on the basis of the pathologic findings.

**SURGERY**—With a fibroma, thecoma, Brenner tumor, or cystic teratoma a conservative surgical removal of just one ovary is sufficient treatment. In the benign pseudomucinous tumor removal of the entire ovary is indicated.

The treatment of the serous cystadenoma is slightly more difficult for these tumors are bilateral in over one half the instances. If they are not obviously bilateral at the time of operation and only one ovary is removed, it is not at all uncommon for tumor to appear in the opposite ovary. A unilateral apparently benign tumor warrants conservative surgery with conservation of the opposite ovary particularly in the young patient. An obviously malignant tumor demands the most radical approach with hysterectomy and bilateral salpingo-oophorectomy. If bilateral tumors of the serous variety are clinically malignant then a radical hysterectomy and bilateral salpingo-oophorectomy are obviously necessary.

If the tumor is a dysgerminoma or an arrhenoblastoma then in most instances a radical rather than conservative approach is indicated. Krukenberg tumors which are diagnosed at operation do not justify any surgical intervention. A questionable sarcoma should be treated by the most radical surgery. It is true that in spite of the clinical history and a careful examination plus all the other possible diagnostic procedures it may be impossible to determine the type of tumor. In this instance, the surgical treatment depends on the training and judgment of the surgeon and pathologist in attendance.

**ROENTGENTHERAPY**—Postoperative radiotherapy is not indicated for any of the benign tumors such as thecomas, Brenner tumors, fibromas, cystic teratomas and serous or pseudomucinous adenomas. If the entire surgical removal of a primary malignant tumor has been accomplished postoperative radiotherapy does not improve the results.

It is unfortunate that ovarian tumors are so often grouped together in the literature without regard to their pathologic type. This is particularly regrettable in view of the fact that the individual types vary considerably in their response to irradiation.

The dysgerminoma is apparently very radiosensitive and therefore if there is any question as to whether it has been completely removed at operation, irradiation is indicated (Menetrier Moreton). There is some cause to believe that granulosa cell tumors are also radiosensitive so that if these tumors have not been completely removed if it is impossible to remove them or if recur

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a large intermediate unpredictable group some of which appear unquestionably malignant and behave in a benign fashion, and vice versa.

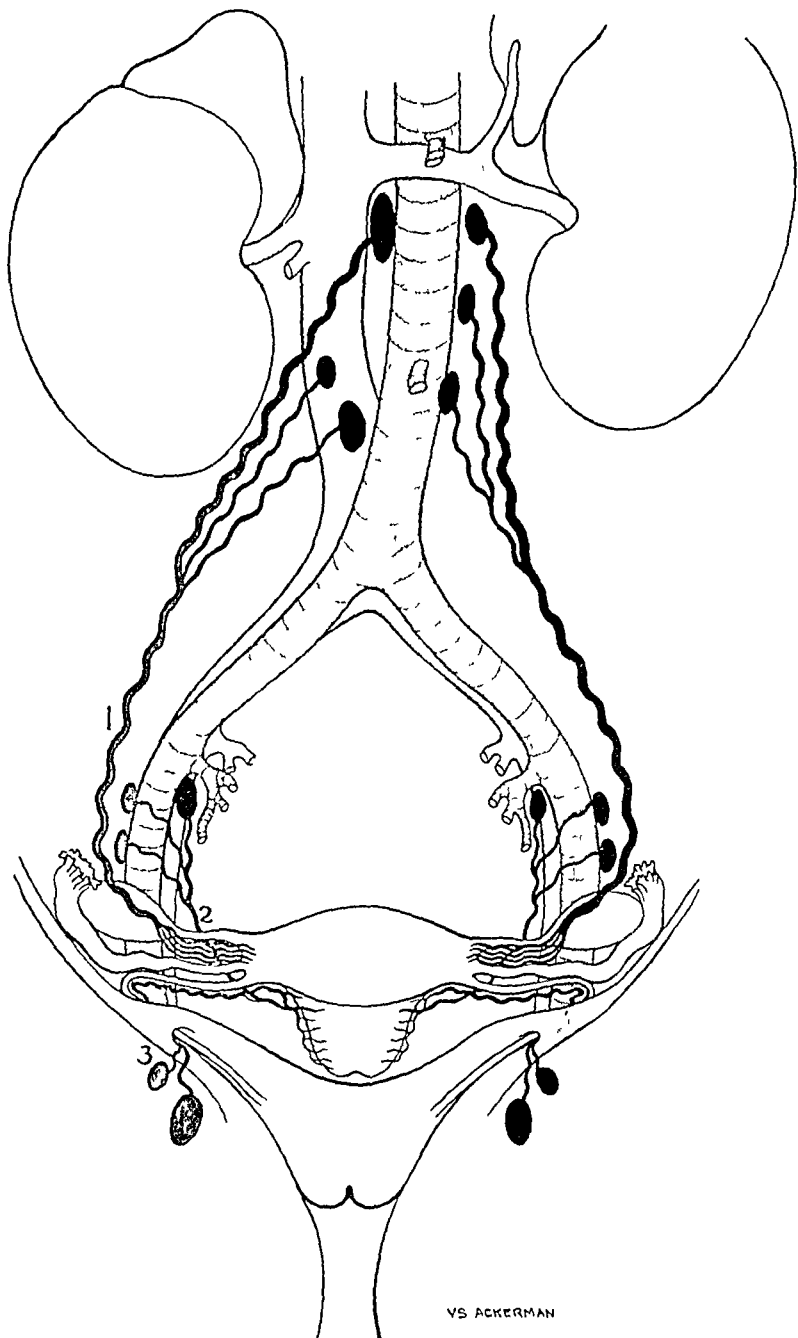
Taylor reported sixty-three cases of primary serous adenocarcinoma with nine five-year cures and twenty-nine cases of pseudomucinous adenocarcinomas with five five-year cures. There were sixty patients with papillary cystadenomas of the ovary between 1910 and 1935 not one of whom had a recurrence. Four of these cystadenomas had peritoneal implants at the time of operation and six were called cancer by the pathologists. Twenty-six of the sixty were borderline lesions but in some of them were classified as malignant the five-year survival for cancer of the ovary would become much higher. Taylor divided his patients with ovarian carcinomas into three groups. In Group I in which it was possible to do complete surgical removal twenty or forty-four were cured. In Group II in which only partial surgical removal could be done two of fifty were cured. In Group III in which exploration alone was possible twenty-nine were explored and none was cured.

Of 100 cases of ovarian tumors reported by Kerr and Einslein, ninety-five were malignant and were treated by surgery and postoperative irradiation. There was a 40 per cent five-year survival. Forty-eight patients died within three years after irradiation and thirty-three of these died in the first eighteen months. There were none who died between three and five years after treatment. Kerr and Einslein divided their cases into four groups. In Group I in which the primary tumor could be removed, there were twenty-one patients ten of whom survived over five years. In Group II in which it was not possible to remove all of the tumor there were forty-eight patients with eighteen survivals. In Group III there were eight cases representing recurrence of malignant tumor following operation or irradiation, and only one patient survived over five years. Group IV consisted of seventeen absolutely inoperable cases, only three patients of which survived five years.

There are some other findings which do have a bearing on the prognosis. If the carcinoma is of the serous variety and contains psammoma bodies the prognosis is enhanced (Healy). If the carcinoma is bilateral the prognosis is much worse. Certainly in a great many instances the extent of the tumor when first seen determines the prognosis. An unsuccessfully treated carcinoma of the ovary usually causes death within the first two years of operation. The five-year survival varies from 10 to 40 per cent.

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Fig 565.—Schematic representation of the lymphatics of the uterus showing 1, the utero-ovarian pedicle 2, the external iliac pedicle and 3, the round ligament pedicle leading to the inguinal lymph nodes

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## CARCINOMA OF THE UTERUS

### Anatomy

The uterus is a pear-shaped muscular organ, slightly flattened antero-posteriorly situated in the midline of the female pelvis between the bladder and the rectum. It is about 7.5 cm long and 5 cm wide. The uterus is attached to the lateral walls of the pelvis by means of the broad ligaments anteriorly by the round ligaments and posteriorly by the uterosacral ligaments. The walls of the uterus are largely composed of thick layers of muscular fibers. Anteriorly the uterus is in almost direct relation to the bladder, posteriorly it is in close contact with portions of the small intestine and with the rectum. The uterus may be divided into the fundus or superior portion, the corpus or intermediate section, and the cervix or lower portion.

The uterine cavity is a triangular space which extends from the cervical canal to the tubal orifices (cornua). This cavity is lined by the *endometrium*, a mucous membrane of simple columnar epithelium containing numerous glands which extend deeply into the thickness of the muscle. The endometrium is about 2 mm thick at the fundus becoming thinner on the corpus and still thinner (0.5 mm) as it approaches the cervix. At the endocervical canal the endometrium becomes smooth and more resistant. The endometrial mucous membrane undergoes physiologic hyperplasia and is periodically eliminated during menstruation.

**Lymphatics**—The uterus has several intercommunicating lymphatic networks which run in the mucosa, muscularis and the serosa and subserous areas,



os and retention of fluid bring about irritating effects on the mucosa which could lead to abnormal cell growth and the production of carcinoma (Healy). Crossen believes that as a rule patients with carcinoma of the endometrium have had a late menopause. The physiologic limits of the menopause are difficult to establish. The age at cessation of menstruation is of relative value, but a comparison of the given ages at this physiologic point does not reveal but a slight difference between women with carcinoma of the endometrium and those affected with other

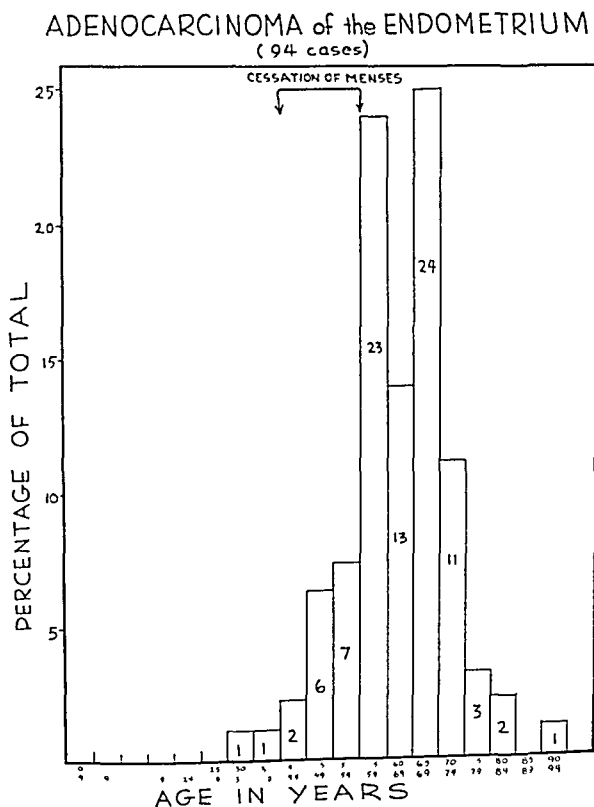


Fig. 566—Age incidence of patients with carcinoma of the endometrium

conditions (Table XLVI). Carcinoma of the cervix is seldom found in nulliparous women, but carcinoma of the endometrium is very frequently found in women who have borne no children. Twenty-seven (28 per cent) of our ninety-four patients with carcinoma of the endometrium had never borne children (Table XLVIII).

The literature contains a variable but consistently high incidence of uterine myomas coexistent with carcinoma of the endometrium (Norris, Stacy). Masson found an incidence of 36 per cent of uterine myomas in 590 patients operated on

the latter receive the lymph from the others, thereby becoming a point of origin for the collecting trunks. The collecting trunks originate in the lateral borders of the uterus and group themselves into three main pedicles (Fig 565).

1 *The utero ovarian pedicle* starts below the uterine tube and travels in the broad ligament until it reaches the hilum of the ovary. Here there are wide anastomoses with the lymphatics of the tube and ovary, and they proceed to the preaortic and lateroaortic lymph nodes on the left and to the precrural and laterocaval lymph nodes on the right.

2 *The external iliac pedicle* contains a lesser number of trunks which follow a transversal direction outward and end in the lymph nodes of the external iliac group.

3 *The round ligament pedicle* is composed of a small number of trunks which follow the round ligament from its insertion in the uterine fundus to the inguinal canal and end in the superficial lymph nodes of the inguinal region.

Consequently the lymphatic drainage of the body of the uterus may finally terminate in the para aortic, paracaval, the external iliac and the inguinal nodes (Testut, Rouviere).

### Incidence and Etiology

Carcinoma of the endometrium is much less frequent than carcinoma of the cervix. In our hospital there is approximately one carcinoma of the endometrium for every five carcinomas of the cervix and at the Pondville State Cancer Hospital a relationship of one to five was also reported by Meigs. A smaller proportion of carcinomas of the endometrium has been reported from other institutions.

Carcinoma of the endometrium usually appears in aged women. Masson studied 732 cases, of which 75 per cent were 50 years of age or older. Only one patient was below 30 years of age, and only 3 per cent were between 30 and 39 years. There is a definite variance in the age incidence of carcinoma of the endometrium and carcinoma of the cervix (Fig 566). We have also found a difference in the proportion of Negro women who have carcinoma of the cervix (10 per cent) and those with carcinoma of the endometrium (5 per cent).

The overwhelming majority of carcinomas of the endometrium develop after the menopause. In ninety-four cases seen at the Ellis Fischel State Cancer Hospital during its first six years, only six developed before cessation of menstruation (Table XVI). It is possible that the obliteration of the cervical

TABLE VII. COMPARISON OF AGE AT CESSATION OF MENSTRUATION IN VARIOUS CONDITIONS IN PATIENTS AT ELLIS FISCHEL STATE CANCER HOSPITAL (NOTE SLIGHTLY GREATER INCIDENCE OF LATE MENOPAUSE AMONG PATIENTS WITH CARCINOMA OF ENDOMETRIUM)

	NUMBER OF POST-MENOPAUSAL PATIENTS	AGE AT CESSATION OF MENSTRUATION				
		UNDER 40	40-44	45-49	50-54	55 OR OVER
Benign gynecologic condition	100	6%	20%	33%	30%	8%
Carcinoma of cervix	191	6%	24%	40%	28%	4%
Carcinoma of endometrium	74	9%	12%	33%	39%	7%
Carcinoma of breast	241	14%	20%	23%	31%	5%

\*Only cases with the necessary data are included.

†According to patients' declaration. Percentages rounded for clarity.

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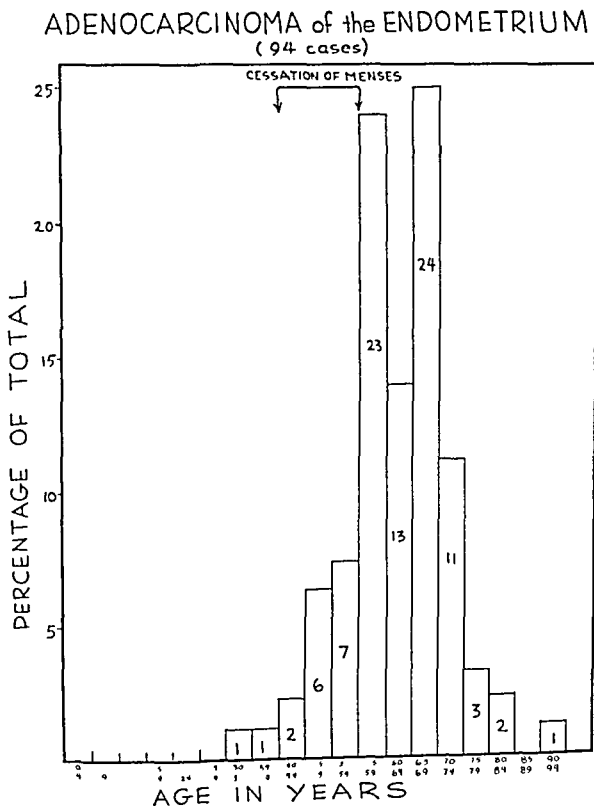


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TABLE XLVII COMPARISON OF PATIENTS AT THE ELLIS FISCHER STATE CANCER HOSPITAL SUFFERING FROM DIFFERENT CONDITIONS IN RELATION TO THEIR WEIGHT (NOTICE HIGH PROPORTION OF OBESSE PATIENTS AMONG THOSE WITH CARCINOMA OF ENDOMETRIUM)

	NUMBER OF CASES*	WEIGHT IN POUNDS ON ADMISSION†			
		UNDER 100	100-149	150-199	200 OR MORE
Adenofibromas and chronic mastitis	105	7%	71%	19%	3%
Carcinoma of the breast	377	8%	57%	30%	5%
Benign gynecologic conditions	188	4%	60%	30%	6%
Carcinoma of the cervix	417	10%	61%	24%	5%
Carcinoma of the endometrium	91	2%	42%	36%	20%

\*Only cases with the necessary data are included

†Percentages have been rounded for clarity

for carcinoma of the endometrium. Some authors believe that the trauma of pre-existing myomas may be a factor in the production of carcinoma of the endometrium.

Patients with carcinoma of the endometrium present a high incidence of obesity (Table XLVII), diabetes, and hypertension. These factors have been incidentally mentioned in the literature but they have not been widely noticed and recorded. Hoffman has stated that overnutrition is an underlying cause of cancer. Dublin found an increased mortality from cancer with the increase in weight of life insurance policyholders. Tannenbaum concluded that a correlation between weight and cancer exists for some types of tumors but not for all. Moss made a special study of this subject in our hospital and found that over 60 per cent of the patients with carcinoma of the endometrium presented heavy weight lateral body build. The incidence of diabetes was found to be very high of his twenty-three patients, five presented a relatively severe diabetes, four were moderate diabetics, and six had a mild diabetes. Of these twenty-three patients Moss found a family history of diabetes in four and an abnormally high blood pressure in eighteen.

The relation of carcinoma of the endometrium to endometrial hyperplasia is debatable. Undoubtedly, hyperplasia of the endometrium can coexist with endometrial carcinoma and Novak believes that transitions between the two can be demonstrated. In 104 cases of adenocarcinoma of the endometrium he found twenty-five with coexisting hyperplasia. Telande has pointed out that there is no absolute criteria for the diagnosis of hyperplasia. He studied the material of Novak and Yun and found the interpretation of these authors more liberal than his own. Telande also pointed out that if hyperplasia is a pre-cancerous lesion a parallelism between the age incidence of hyperplasia and carcinoma should be expected. On the contrary, the incidence of hyperplasia of the endometrium decreases and the incidence of carcinoma increases after 50 years of age. Payne studied 534 patients with endometrial hyperplasia, of whom 496 were premenopausal and 38 postmenopausal. The incidence of co-existing carcinoma and hyperplasia was 2.4 per cent and was five times more frequent in the postmenopausal group than in the premenopausal group. Taylor reported 85 cases of endometrial hyperplasia, 2 of which had developed into adenocarcinoma, but in both instances the apparent transformation was due to failure to detect the carcinomas on first examination.

Estrogen-secreting ovarian tumors are not infrequently accompanied by carcinoma of the endometrium. There is a high correlation between thecomas and granulosa-cell tumors of the ovary on one side and endometrial hyperplasia and adenocarcinoma of the endometrium on the other side. Most authors agree that the hyperplasia in these cases results from unopposed estrogenic effects, and since the hyperplasia is considered as precancerous, it is easy to understand why an excess of estrogens is considered as a cause of the coexistent carcinoma of the endometrium which is sometimes found in these cases. But carcinoma of the endometrium has occurred in surgically castrated women. Smith reported 3 cases occurring fifteen years after bilateral oophorectomy. This means that the direct relationship of estrogens and carcinoma is still an open question (Ingraham). McGoldrick collected forty-six cases of *theca-cell tumor of the ovary*, thirty-six of which presented hyperplastic changes of the endometrium, thirty-two of these after the menopause. There were five coexistent endometrial carcinomas in the postmenopausal group. *Granulosa-cell tumors* of the ovary may also be associated with adenocarcinomas of the endometrium and they very frequently show endometrial hyperplasia (Ingraham). There is on record a case of granulosa-cell tumor with coexistent carcinoma of the endometrium (Stohr) in which the carcinoma disappeared after surgical removal of the granulosa-cell tumor. There is some question, however, as to whether this was a true carcinoma or marked endometrial hyperplasia. The same doubt may be extended to the authenticity of some cases of coexistent carcinoma of the endometrium and estrogen-secreting ovarian tumors.

Carcinomas of the endometrium may arise from pre-existing endometrial polyps (Iseki). *Sarcomas* of the uterus are rather infrequently observed, making up only about 4 per cent of all malignant tumors of the uterus. They are found in patients 40 to 60 years of age. A high proportion of sarcomas arise from pre-existing leiomyomas (Masson).

### Pathology

**Gross Pathology**—Endometrial carcinomas are usually flat, velvet lesions arising from the walls of the corpus, from the fundus, or in the region of the cornua. Sometimes they appear pedunculated. The lesions are usually well circumscribed and grow toward the endometrial cavity, but in some cases they are diffusely infiltrating. By direct invasion the tumor may ulcerate the cervix and extend to the vaginal fornices. It may also invade the myometrium, increasing the size of the uterus and producing necrotic excavations. Invasion of the serosa, the parametria, bladder, and small and large intestine may occur in advanced cases.

Extension of the tumor to the region of the cornua and Fallopian tubes may result in direct invasion of these structures or in a tumor embolism leading to a separate growth (Lynch).

Crossen has proposed a classification of carcinomas of the endometrium on the basis of gross and microscopic pathologic findings.

*Stage I*—The tumor is limited to the surface and has not yet invaded the muscular layers (Fig 567)

TABLE XLVII COMPARISON OF PATIENTS AT THE ELLIS FISCHER STATE CANCER HOSPITAL SUFFERING FROM DIFFERENT CONDITIONS IN RELATION TO THEIR WEIGHT (NOTICE HIGH PROPORTION OF OBSE PATIENTS AMONG THOSE WITH CARCINOMA OF ENDOMETRIUM)

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*Stage II*—There is definite involvement of the muscular layers but it is limited to the inner half of the myometrium (Fig 568)

*Stage III*—There is extension to the outer half of the muscular layers including possible invasion of the serosa (Fig 569)

*Stage IV*—There is extension of the tumor outside the uterus in the parametrium, or there is an operable metastatic implant in the ovary. This may include inflammatory adhesions to the intestines or bladder in which microscopic examination has eliminated the possibility of carcinomatous invasion of such organs (Fig 570)



Fig 571—Carcinoma of the endometrium with extension to the bladder and rectum (Stage V Crossen)

*Stage V*—There is extension to adjacent removable organs, the carcinomatous invasion of such organs to be verified microscopically (Fig 571)

*Stage VI*—There is regional extension or distant metastases beyond the scope of surgical removal (Fig 572)

This detailed classification may be very usefully applied to operable cases. It has a disadvantage in that it loses most of its merit when applied to tumors which have received extensive irradiation before hysterectomy. Also, it ob-

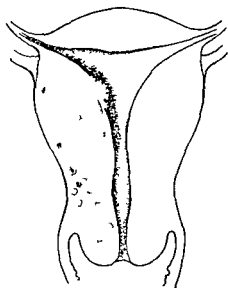


FIG 567

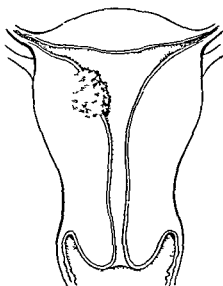


Fig 568

Fig 567—Early carcinoma of the endometrium without invasion of the muscular layer (Stage I Crossen)

Fig 568—Carcinoma of the endometrium with involvement of the muscular layer limited to the inner half of the myometrium (Stage II Crossen)

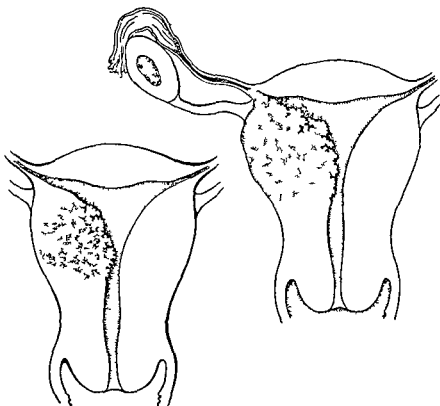


Fig 569

Fig 570

Fig 569—Carcinoma of the endometrium with extension to the serosa throughout the muscular layers (Stage III Crossen)

Fig 570—Carcinoma of the endometrium with invasion of the serosa and with operable metastases to the ovary (Stage IV Crossen)



*Sarcomas* usually arise in the center of leiomyomas. Here the benign tumor becomes soft and grayish-white. In a group of fifty sarcomas reported by Novak, thirty-nine arose from myomas and eleven arose from the uterine wall. They may also arise from the endometrium (Fig 573).

**Metastatic Spread**—Lymphatic metastases from carcinomas of the endometrium usually do not appear until the disease is moderately advanced. They involve the external iliac and para-aortic chains and also the inguinal lymph nodes. Retrograde metastases through the vaginal mucosa may result in metastatic implants in the lower third of the vaginal wall and vulva. Distant metastases are observed in advanced cases and may be found in the liver, lungs, brain, and bones. *Sarcomas* metastasize widely through the blood stream, most commonly to the liver and lungs.



Fig 573—Sarcoma of the uterus. Patient died with extensive metastases six months after operation.

**Microscopic Pathology**—Whether carcinomas of the endometrium arise or not from pre-existing hyperplasia, the fact is that the two are often associated, and for this reason it is important to be able to differentiate them. The term endometrial hyperplasia was introduced by Novak in 1915, establishing a difference with the so-called endometrial hypertrophy which was thought to be another entity. In endometrial hyperplasia there is marked glandular proliferation. The glands may be lined by several layers of cells, and there may even be some invasion of the muscle. The deeper glands may show cystic dilatation which gives it a typical appearance that has been called "swiss cheese endometrium" by Novak (Fig 574). Herrell and Broders prefer the term cystic endometrium, and in their opinion sudden withdrawal or dysfunction of the ovarian tissue is usually accompanied by atrophy of the endometrium. How-

viously cannot be used for the inoperable cases, which constitute a sizable number of all cases of carcinoma of the endometrium

A small number of cases (about eighty five) have been reported in which carcinoma arose from a polyp Tahlund, in a study of 236 cases of postmenopausal uteri, found an incidence of polypi of the endometrium which was roughly eight times greater in the cases which had carcinoma than in those without this case Polyps arise near the region of the cornua and are often observed after the menopause They are usually well vascularized and may overlie a submucous leiomyoma

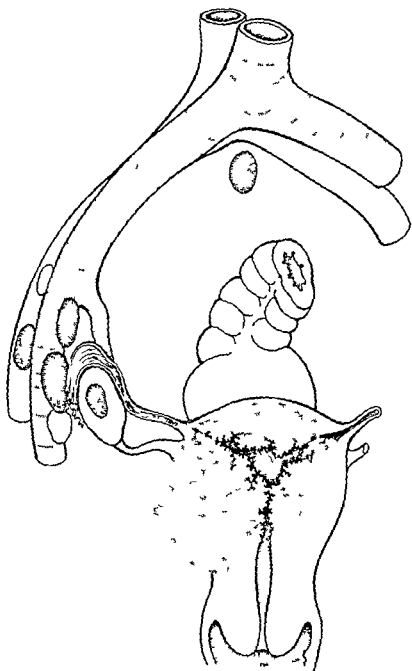


Fig 5 —Carcinoma of the endometrium with extension outside the uterus metastases to the ovary and external iliac nodes and to the nodes of the promontory (Stage VI Crossen)

ever, many an endometrium removed after menopause histologically resembles that found in an active period of menstrual function (Novak and Richardson) In 236 cases of postmenopausal uteri studied by Fahlund, 41 per cent of those which contained carcinoma of the endometrium presented an atrophic endometrium, while only 16 per cent of those without carcinoma had an atrophic endometrium Approximately 42 per cent of the cases with carcinoma showed no cystic changes, while only 20 per cent of those without carcinoma showed no cystic changes

As a rule, pure endometrial hyperplasia is not difficult to differentiate from adenocarcinomas of the endometrium The hyperplasia presents a velvety thickened endometrium which may involve the entire cavity but stops abruptly at the internal os Microscopically, unlike carcinoma it shows no areas of necrosis and it reveals areas of hyperplasia of both the stroma and the glands with numerous cystic areas (Fig 575) In a very limited number of cases it may be difficult to distinguish it from carcinoma

The grading of carcinomas of the endometrium presents definite difficulties because it is not unusual to find different degrees of differentiation in several separate specimens removed These tumors should be graded according to the most malignant variation The classification of Healy and Cutler is excellent They divided the cases into four groups to represent gradings of potential malignancy

*Grade I Papillary Adenoma Malignum*—The growth is superficial and entirely papillary The cells are not atypical and there is no infiltration This is the least malignant of the group Some cases have been reported cured by simple curettage

*Grade II Adenoma Malignum*—There is marked enlargement of the uterine glands which are thrown into folds to form papillae The nuclei are hyperchromatic and mitoses may be abundant The cells should have no tendency to form solid masses or to infiltrate the stroma (Fig 10)

*Grade III Adenocarcinoma*—The tumor forms solid masses of cells in cords and columns with loss of polarity and infiltration of the stroma The cells are fairly atypical, but the glandular arrangement is maintained

*Grade IV Embryonal Anaplastic or Diffuse Carcinoma*—There is complete loss of polarity and of glandular arrangement The cells are small, round, polyhedral, and closely packed and grow in sheaths or cords There are marked signs of anaplasia, no differentiation, and abundant mitoses These cases may be difficult to differentiate from anaplastic epidermoid carcinomas of the cervix

To these may be added the rare *adenocanthoma* which presents mixed features of epidermoid carcinoma and adenocarcinoma The more complicated morphologic classifications such as that of Heyman and Reuterwall are not practical

*Sarcomas* arise most commonly from pre-existing leiomyomas, but they can derive from any mesodermal tissue such as smooth muscle, blood vessels, and connective tissue Designations such as round-cell, spindle-cell, or giant-cell



Fig. 3. Low-power photomicrograph of endometrial hyperplasia showing typical cystic and tubular glands (very low cellular content).



Fig. 4. High-power photomicrograph of the same area as in Fig. 3, showing a large, irregular, and highly cellular mass, likely representing a malignant tumor.

**Clinical Examination**—Before an examination is started a careful menstrual history should be recorded, the absence or presence of pain and its character, as well as other symptoms should also be investigated. It should not be forgotten that obese multiparous patients presenting diabetes and hypertension frequently develop carcinoma of the endometrium.

A thorough bimanual examination should be done in an attempt to establish the size of the uterus and its mobility. Because of obesity, the palpation may fail to reveal the actual size of the uterus or it may be handicapped by pain or lack of cooperation on the part of the patient. In such instances an examination under anesthesia may be indicated. The examination moreover is useful to establish the differential diagnosis with ovarian tumors.

In the majority of cases of carcinoma of the endometrium, the cervix shows no involvement, but in some instances there may be an ulceration extending to the vaginal walls. Retrograde metastases of the vaginal wall, particularly around the urethra, may be detected. In general, the parametria will not be found invaded except in very advanced cases.

**Biopsy**—In most instances a diagnosis is only possible after dilatation of the cervix and curettage of the uterine cavity. There should be no hesitation in carrying out this procedure in all cases of unexplained postmenopausal vaginal bleeding. It should be kept in mind however, that this method carries some danger of perforating the uterus. A curettage of the uterus should secure tissue from the fundus corpus, and endocervix, tissues which should be kept separately if possible.

The pathologic study of vaginal smears has been proposed as a means of diagnosis (Papanicolaou). But the study of vaginal smears, while relatively simple, is time consuming and requires considerable experience in interpretation (Gates, 1945). It has been claimed that vaginal smears may be positive in cases where a curettage is reported negative but these cases are few. With vaginal bleeding, a curettage of the endometrium is a considerably more adequate diagnostic procedure. Cervical smears are probably indicated and should be restricted to studies of asymptomatic women in whom a routine dilatation and curettage is not justified. The procedure may become very useful in routine examinations for purposes of detection of early carcinomas.

**Clinical Classification**—A clinical classification of carcinoma of the endometrium (comparable to the League of Nations' classification of carcinoma of the cervix) is desirable, but although several have been suggested they are far from being as valuable in the prognosis as the one for carcinoma of the cervix. Healy has pointed out that uterine enlargement in carcinomas of the endometrium has prognostic significance when radiotherapy alone is to be given. But the evaluation of the size of the uterus is a relative one, particularly in view of the fact that leiomyomas often accompany these tumors. Bowing and Fricke have proposed a purely clinical classification in four stages.

*Stage I*—Uterus not enlarged and movable

*Stage II*—Uterus enlarged but movable

sarcoma are not justified because they do not indicate histogenesis. It is true that in many instances the extensive growth of the tumor has blotted out any chance of determining histogenesis, but the majority are leiomyosarcomas.

### Clinical Evolution

Early symptoms of carcinoma of the endometrium may not be unduly marked but because they most commonly occur after the menopause they cause immediate alarm. The most common early sign of disease is a slight vaginal *bleeding*, which may remain minimal but also may be shortly followed by a marked *hemorrhage*. Watery discharge, extremely malodorous is at times present and is a very significant sign of the disease. In some instances there may be spontaneous elimination of small fragments of friable tumor. Complaints of *menstrual pains* are often due to retention of blood or fluid and to the resulting uterine contractions. Pain is not an early symptom. When it appears it is persistent and progressive, spreading from the lumbar region around the lower abdomen and radiating to the hips and thighs. *Urinary symptoms* are seldom present and compression of the ureter and *anureas* are less frequently observed than in carcinoma of the cervix. *Constipation* is caused by mechanical pressure over the rectosigmoid when the tumor becomes voluminous.

Most carcinomas of the endometrium develop slowly and even though the disease may be considerably advanced the patients may survive for years in a rather good general condition. Inertia may be present in markedly bleeding tumors. Death often occurs as a consequence of hemorrhage. Grigoutoff in a study of 110 cases of carcinoma of the endometrium found an unusually high percentage with metastases (about one third of his cases). The majority of these were vaginal, vulvar, in utero and intra-abdominal metastases, but there were four cases of pulmonary metastases, two of intracranial metastases and one of bone metastases.

Surgical development slowly and usually discharge or bleeding after they invade the endometrium. Advanced cases are accompanied by severe pain. General nature of the disease is more common than in carcinoma.

### Diagnosis

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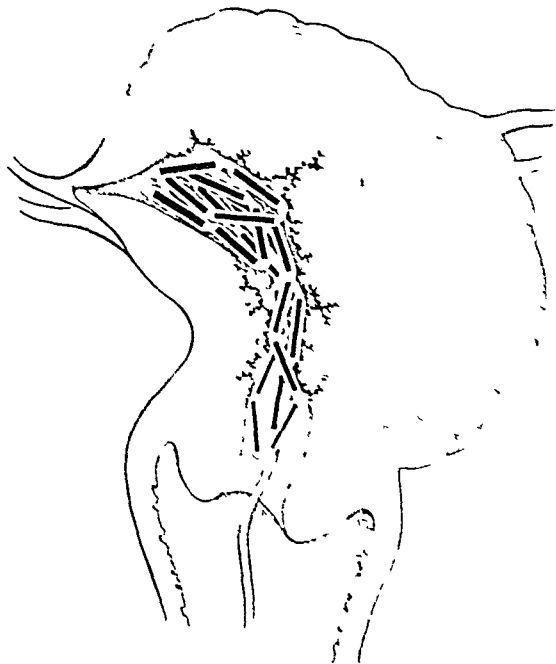


Fig. 576—Intracavitary irradiation of oral cavity by means of a flexible catheter containing neodymium yttrium salts (diaplyat). Note that the cavity is far in the center of the tumor and consequently irradiation cannot be homogeneous.

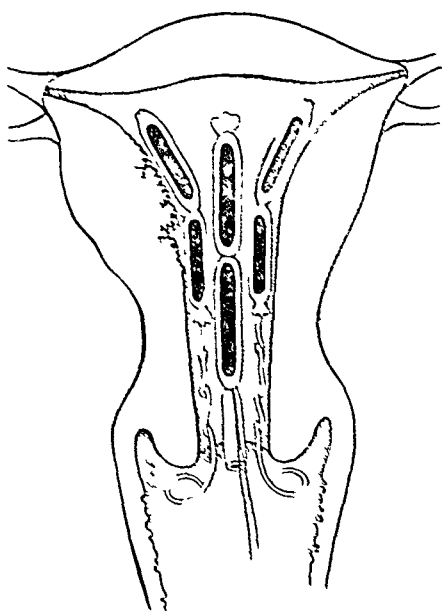


Fig. 577—Technique of administering intracavitary curietherapy for carcinoma of the endometrium by means of Grossman's distributor.

*Stage III—*

a Uterus not enlarged but with limited mobility and infiltration of both parametria

b Uterus enlarged and fixed with infiltration of an entire parametrium (out to the pelvic wall)

c Uterus enlarged or not with involvement of the cervix with or without vaginal invasion

*Stage IV—*Uterus enlarged and fixed, evidence of extrapelvic metastases

In cases which are being curetted it is of value to make note of the dimensions of the uterine cavity. This additional information may aid in the classification (Miller)

**Differential Diagnosis—**Speculum examination easily reveals those cervical lesions which may cause vaginal bleeding (*carcinoma of the cervix, cervical polyps*). A thorough bimanual palpation, particularly if it is carried out under anesthesia, can reveal the presence of an *ovarian tumor*. A dilatation of the cervix with curettage of the endometrium facilitates the diagnosis of *endometritis*, *prometria*, *endometrial hyperplasia*, and *endometrial polyps*. *Submucous leiomyomas* may also be diagnosed by curettement. When *sarcomas* have invaded the endometrium, they too may be diagnosed from curettings. The presence of *leiomyomas* which may be felt on palpation does not eliminate an additional possibility of *carcinoma* of the endometrium. The association of both is rather frequent (Marrin)

**Treatment**

In the past, three important facts seem to have found wide assent in the treatment of carcinomas of the endometrium: (1) that the best results are obtained when a hysterectomy is practicable, (2) that the results are considerably improved by preoperative radiotherapy, and (3) that a large proportion of the inoperable cases can be cured by a skillful application of radiation therapy. Heyman stands as a courageous lone dissenter. To him radiotherapy is the treatment of choice and a hysterectomy should be done only if radiotherapy has failed (11 per cent in his series). He supports this view with convincing excellent results in both the operable and the inoperable patients.

**RADIOTHERAPY—**A preoperative irradiation of the uterus is definitely useful. Healy suggested that patients with adenoma malignum (Grades I and II) be operated without previous irradiation, but these cases are very few and preoperative irradiation is not necessarily contraindicated. Consequently, it can be postulated that preoperative irradiation is indicated in all cases of carcinoma of the endometrium. Preoperative irradiation diminishes considerably the secondary infection and the volume of the tumor, facilitating its extirpation and in all probability diminishing the possibilities of postoperative recurrence and metastases.

The most widely used means of preoperative irradiation has been the intrauterine curietherapy, but a thorough external pelvic roentgentherapy may be equally valuable and may be used to advantage as an adjunct to intracavitary curietherapy (Miller). When irradiation is not to be followed by a hysterectomy



different techniques proposed, he concludes that Heyman's method allows a better distribution of radiations

In judging the effect of preoperative irradiation, the pathologic examination of the surgical specimen is of great value, but the conclusions reported in the literature on the basis of this study are confusing. The fact that tumor is found remaining in the uterus following preoperative irradiation cannot be taken as a measure of the usefulness of this therapeutic step. On the other hand, the ability to find remaining persistent carcinoma depends on the thoroughness of the microscopic search. Obviously, a total disappearance of the tumor cannot be expected when surgery is done immediately after completion of the

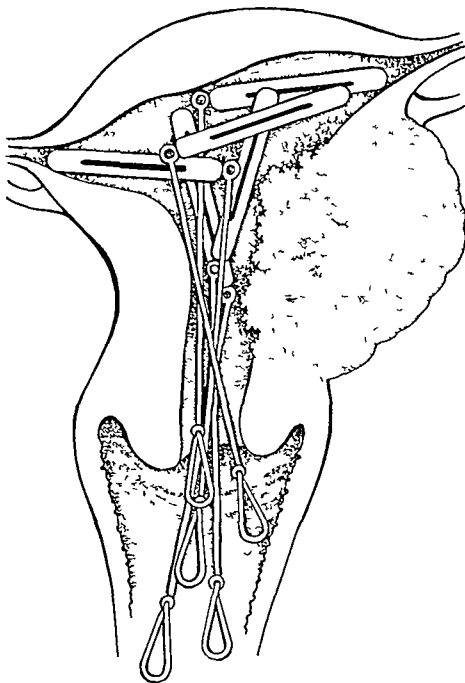


Fig. 579—Technique of intracavitary curietherapy by means of specially devised applicators to facilitate angular positions (Martin)

irradiation, all tumors, even the most radiosensitive, have a more or less prolonged period of latency before complete dissolution. On the other hand, a hysterectomy done several months after radiotherapy will show obvious evidence of recurrence if the amount of radiations has been insufficient to sterilize it. In general, however, the preoperative radiotherapy is given without intent of totally sterilizing the tumor, and to delay surgery is not justified. Sheehan has made a very thorough study of the effects of radiotherapy on carcinoma of the endometrium. He found almost constantly a plaque-like area of coagulation necrosis at the internal os, zones of hyalinization and edema of the myometrium, and some degree of endometrial hypertrophy.

tomy, the intracavitary curietherapy should be preceded by a thorough external pelvic roentgentherapy in order to insure, as far as possible, a homogeneous irradiation of the entire tumor area. This external pelvic irradiation may also be beneficially used in the operable cases.

The intracavitary curietherapy of the uterus affected by carcinoma of the endometrium offers unquestionable difficulties. In general, the uterine cavity is enlarged and the "tandem" containing the radium needles or tubes may not occupy a desirable position in respect to the tumor. In addition, the development of tumor toward one side may greatly interfere with its homogeneous irradiation by internal sources of radiation. Hurdon, Schmitz,

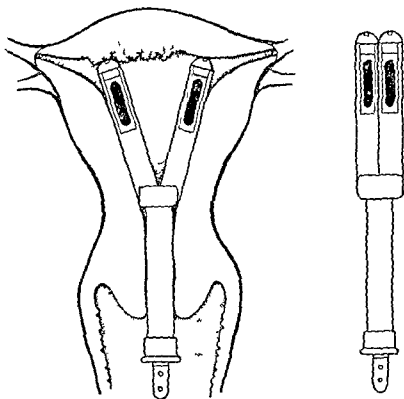


Fig. 578.—Technique of radium application in a carcinoma of the fundus by means of Schmitz's Y-shaped applicator.

Martin, Kaplan, Crossen, and many other authors have suggested different methods in an effort to solve this problem (Figs 576, 577, 578, and 579). Friedman devised an ingenious gadget, the "hysterostat," which has value because of its adaptability to the different shapes and sizes of the uterine cavity (Fig. 580). The simplest and most successful solution of this problem, however, has been that suggested by Heyman, who packs a variable number of "irradiators" into the uterine cavity until it is filled (Fig. 581). Two such applications are given with a three week interval. Heyman reports a very low incidence of perforations of the uterus. These applications may be supplemented by a vaginal irradiation with a special nickel plated brass holder containing radium tubes. The "packing method" in Heyman's hands has given the best results to date. Nolan has done a thorough study of the distribution of radiations in the pelvis with the

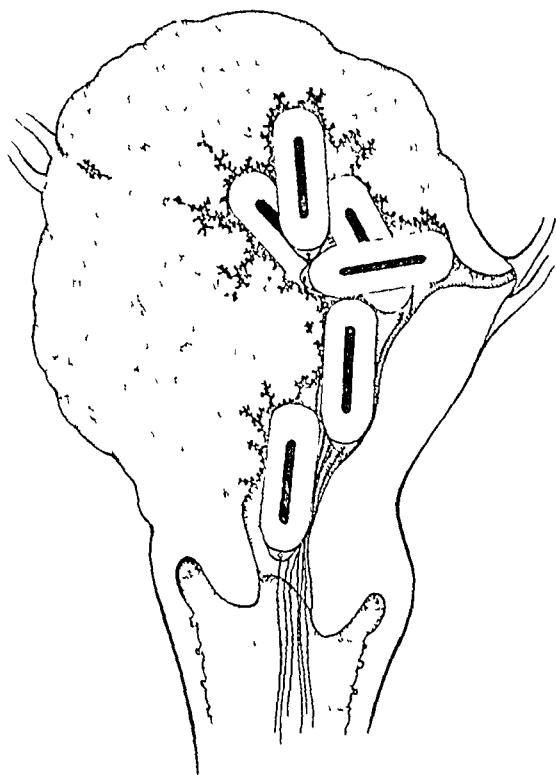


Fig 581—Method of intracavitary curietherapy in an advanced case of carcinoma of the endometrium by means of Heyman's packed irradiators.

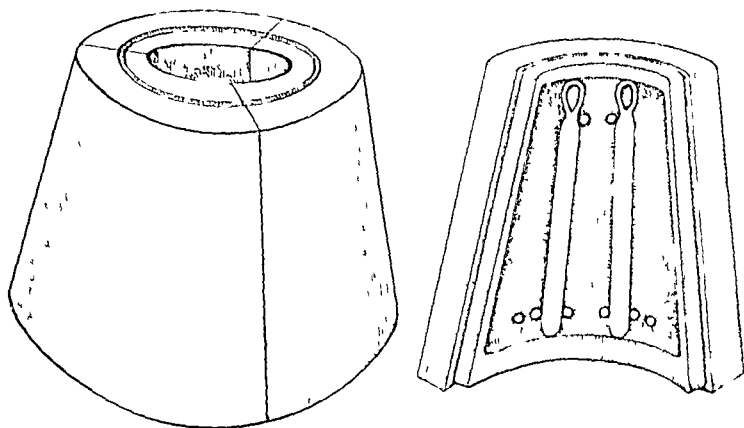


Fig 582—Heyman's applicator for "brachyradium" especially fitting for postsurgical vaginal recurrences following hysterectomy for carcinoma of the endometrium.

Surgical failures are usually due to vaginal recurrences or metastases. The treatment of such recurrences is necessarily variable according to the case. Heyman advises the use of a "brachyradium" treatment by means of a special applicator (Fig 582). Interstitial curietherapy, especially in the form of implants of radium element needles, may be used to advantage in certain cases as vaginal metastases are often the only manifestation of the recurrent disease and their successful handling may save the life of the patient.

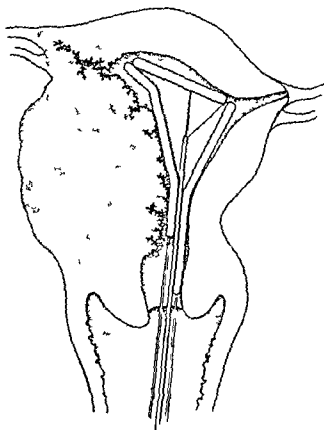


Fig 580.—Method of intracavitary curietherapy in carcinoma of the endometrium by means of Friedman's hysterostat.

**SURGERY.**—An abdominal hysterectomy with bilateral salpingo oophorectomy is preferable in the treatment of tumors of the endometrium. However, a vaginal hysterectomy may be considered in some instances as a second choice. At operation, as large a vaginal cuff as is possible should also be removed. The operative mortality varies greatly but ranges between 5 and 15 per cent. There are a few instances in which an operation without benefit of previous radiotherapy may be indicated.

A large number of cases of carcinoma of the endometrium, perhaps as many as 50 per cent are found to be inoperable. The inoperability may be due to the extension of the tumor outside the uterus but is most often caused by vaginal extension or metastases. Very often patients are judged inoperable on the basis of obesity, hypertension or diabetes. Sarcomas should be treated by a complete hysterectomy whenever possible, without previous irradiation.

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### Prognosis

Adenocarcinomas of the endometrium are very curable, according to Healy, no institution should be satisfied with an over all five year cure rate below 50 per cent. Histologically the adenoma malignum type of tumor has the best prognosis whether it is treated by surgery or by radiotherapy.

Arneson summarized the results obtained in seventeen different clinics and found that of 927 patients treated by *hysterectomy alone*, 57 per cent were well after five years. A similar compilation made by Heyman showed that of 744 patients treated in four different clinics by *hysterectomy alone*, 53 per cent remained well five years.

The results of *radiotherapy followed by hysterectomy* have been very variable and the number treated by each author is very small. Corsecaden collected 598 cases from the literature, 292 of the patients (50 per cent) being reported well at the end of five years. Although this compilation does not show a favorable balance in favor of the combined technique this may be attributed to the fact that there is a tendency everywhere to treat in this fashion the more advanced cases within the operable group. Miller reported on a series of ninety six patients in whom external roentgentherapy alone was used as a preoperative measure instead of or without additional, intracavitary radiumtherapy. A total of sixty one patients (77 per cent) were reported living after five years.

The results of *radiotherapy alone* are surprisingly good, even in the inoperable group. Arneson collected 998 cases from the literature and found a 37 per cent five year survival. At the Radiumhemmet of Stockholm, Heyman treated 316 patients with his "packing method" of intracavitary curietherapy and 183 of these (58 per cent) showed no recurrences within five years, twenty two additional patients were cured by hysterectomy following failure of radiations (a total of 65 per cent five year survivals). But unlike most other series Heyman's includes a large proportion of operable cases. Of 153 operable cases treated by Heyman, 102 (66 per cent) of the patients showed no recurrences within five years, thirteen additional operable patients were cured by hysterectomy following failure of radiations (a total of 75 per cent five year survivals). This substantiates Heyman's prediction (1941) "Should we succeed permanently to obtain in our clinically operable cases by the packing method a cure rate of about 60 per cent, we would be justified in concluding that it is possible to obtain better results by radiotherapy alone than by surgery alone."

It must be emphasized that the prognosis of carcinoma of the endometrium as a whole is a rather favorable one, regardless of methods of treatment. Miller reported that from 322 patients who consulted at the University Hospital at Ann Arbor Michigan, a total of 301 received treatment, and of these, 194 (60 per cent) were well and free of symptoms five years after.

The *sarcomas* which arise in pre existing leiomyomas of the uterus have a variable prognosis, depending upon their degree of differentiation and mitotic activity (Evans). Novak reported a series of fifty patients operated on, fifteen of whom (30 per cent) survived five years and twelve of whom remained well ten years.

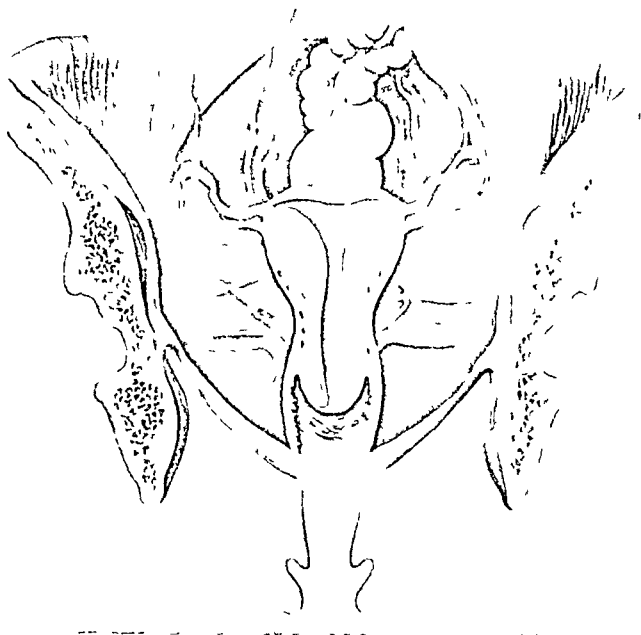


Fig 583 —Anatomic sketch of a frontal section of the pelvis illustrating relative position and size of the uterus



Fig 584 —Sagittal section of the pelvis demonstrating the close relationship of the cervix to the bladder and rectum

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## CANCER OF THE CERVIX

### Anatomy

The cervix, or lower portion of the uterus, is a cylindrical structure which enters the vaginal canal at its superior extremity. Normally the cervix points inferiorly and posteriorly. The vaginal wall forms a circular cul de sac around the cervix which is arbitrarily divided into four *fornices*, one anterior, one posterior, and two lateral. The anterior fornix is represented by a shallow fold. The posterior fornix is the deepest. The cervix has a central orifice, the *external os*, which, in the normal adult multipara is a transversal opening with an anterior and a posterior lip. The external os gives access to the cervical canal.

The cervix is covered by a squamous epithelium which is a continuation of the vaginal mucosa. At the external os, however, this mucosa changes abruptly into an arborescent, more rugous epithelium which is characteristic of the endometrium.

The cervix, like the rest of the uterus is attached laterally to the pelvis by a thin elastic ligament, the broad ligament, which extends from the lateral aspects of the uterus to the pelvic wall and divides the pelvis into an anterior (vesical)



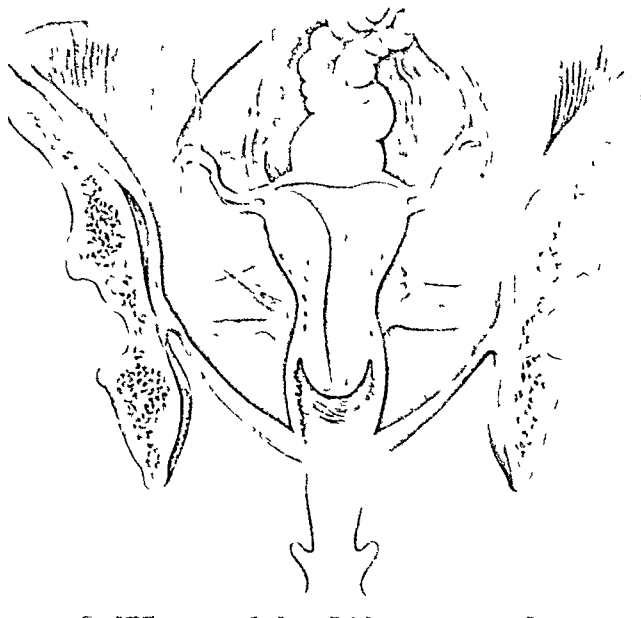


Fig 583 —Anatomic sketch of a frontal section of the pelvis illustrating relative position and size of the uterus



Fig 584 —Sagittal section of the pelvis demonstrating the close relationship of the cervix to the bladder and rectum

and a posterior (rectal) compartment (Fig 585). The broad ligament is formed by two layers of peritoneum which, descending on the anterior and posterior aspects of the uterus and tubes, come in almost immediate contact with each other ("The peritoneum hangs on the tubes as a tablecloth hangs on the line"). Arising from the posterior aspect of the broad ligament there is a pedicle, the *meso ovarium*, which supports the ovary. The portion of the broad ligament which lies above the meso ovarium is called the *mesosalpinx* and that

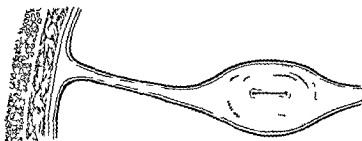


Fig 585—Transverse section of a parametrium and uterus showing division of the pelvis into a vesical and a rectal compartment

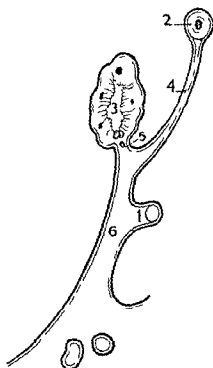


Fig 586—Paramedian section of a broad ligament illustrating 1 round ligament 2 Fallopian tube 3 ovary 4 the mesosalpinx 5 the meso ovarium and 6 the mesometrium or parametrium

which lies below the meso ovarium is the *mesometrium* or *parametrium* (Fig 586). The parametrium contains a rich cobweblike subserous adipose and connective tissue which is continuous with that surrounding the uterus and the one contained in the uterosacral ligaments. It also contains the uterine artery, nerves and numerous lymphatics. The ureters pass through the parametrium in a forward and inward direction and lie about 1.5 cm lateral to the cervix

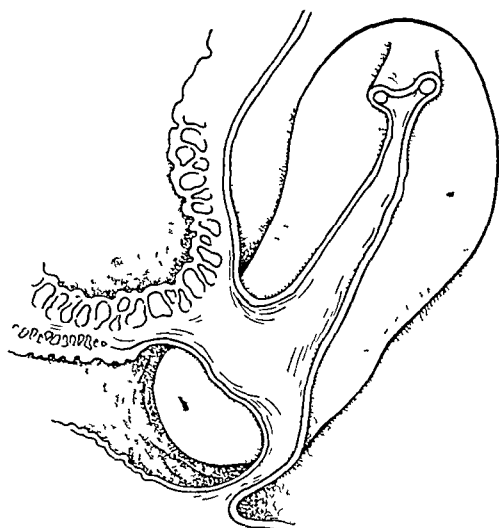


Fig 587—Schematic reproduction of a section of the broad ligament at its insertion into the cervix and lateral aspect of the uterus

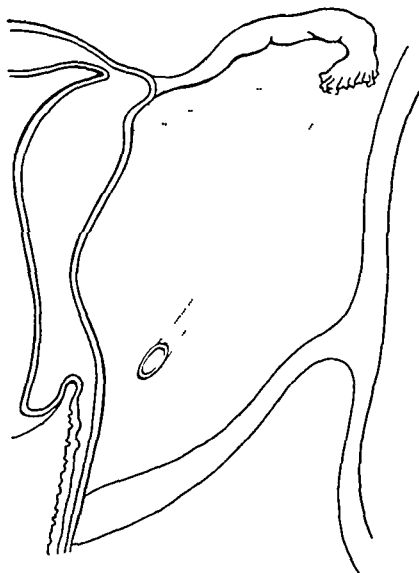


Fig 588—Frontal section of the pelvis showing approximate relationship of the left ureter to the cervix

and a posterior (rectal) compartment (Fig 585) The broad ligament is formed by two layers of peritoneum which, descending on the anterior and posterior aspects of the uterus and tubes, come in almost immediate contact with each other ("The peritoneum hangs on the tubes as a tablecloth hangs on the line") Arising from the posterior aspect of the broad ligament there is a pedicle, the *meso ovarium*, which supports the ovary The portion of the broad ligament which lies above the meso ovarium is called the *mesosalpinx* and that



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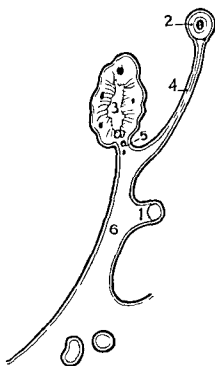


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(Fig 588) The *uterosacral ligaments* are of lesser importance. They are formed by secondary peritoneal folds which extend from the posterior surface of the cervix and isthmus, follow an anteroposterior direction, on either side of the rectum, and end on both sides of the first sacral vertebra. The uterosacral ligaments contain some alveolar tissue, which is continuous with the parametrium at its base, a few arteries and veins, and some lymphatic vessels. They are very elastic structures.

Anteriorly, the cervix is in close relation to the bladder, from which it is separated only by a few millimeters of celluloadipose tissue (Fig 584). Posteriorly, the cervix is separated from the rectal wall only by the posterior fornix.

**Lymphatics**—The lymphatics of the cervix form a rich plexus. This plexus is lateral to the cervix and may present nodularities which have been interpreted as veritable lymph nodes (Lucas-Championnière). From this plexus the lymphatics gather into three main pedicles.

(1) The *preuterine pedicle* follows the direction of the uterine artery, passes in front of the ureters, crosses the internal aspect of the umbilical artery, and ends in the middle and internal groups of nodes of the external iliac chain. This pedicle is designated as the *principal chain* of lymphatics of the cervix (Peiser, Leveuf).

(2) The *retrouterine pedicle* follows the course of the uterine vein, passes behind the ureter, and ends in one of the hypogastric lymph nodes near the uterine artery.

(3) The *posterior pedicle*, less rich and less constant than the other two, follows an anteroposterior direction on each side of the rectum and later traces an upward curve to end in the laterosacral lymph nodes and sometimes reaching the lymph nodes of the promontory (Fig 589).

### Incidence and Etiology

Carcinoma of the cervix is the second most common form of cancer in women. In Negroes, it seems to be more frequent than carcinoma of the breast. At the Homer Phillips Hospital for Negroes in St. Louis, carcinoma of the cervix is five times more frequent than carcinoma of the breast and contributes one-third of all malignant tumors seen there (Blache). Jewish women, who are not immune to other forms of cancer, present a very low incidence of carcinoma of the cervix.

Cancer of the cervix is very infrequently found in women under 20 years of age. Bowing and McCollough reviewed 3,000 cases seen at the Mayo Clinic and found only one patient under that age. They found only twelve other cases reported in the literature. To these, three more have been added (Morehead). Of these fifteen cases, thirteen were found in girls 10 to 20 years old, one was present in a 7-year-old child, and one in a 20-month-old baby. Inasmuch as eleven of these fifteen were reported as adenocarcinomas and that a post-mortem examination was not done in all cases, this suggests that some among them might actually not have been primary carcinomas of the cervix.

Fig 590 shows the distribution by age groups of 453 patients admitted to the Ellis Fischel State Cancer Hospital during its first six years. Only nineteen

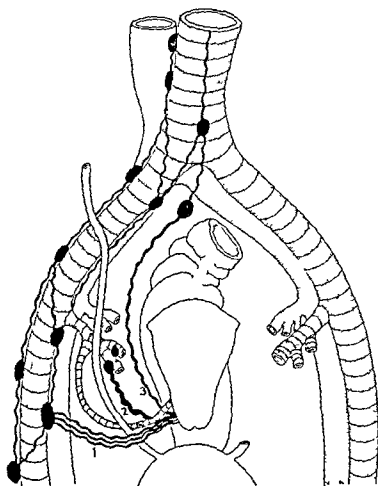


Fig. 589.—Schematic reproduction of the lymphatics of the cervix showing 1 the pre-ureteral or principal chain of lymphatics 2 the retroureteral lymphatics and 3 the posterior lymphatics.

TABLE XLVIII COMPARISON OF PATIENTS WITH DIFFERENT LESIONS ACCORDING TO PARITY  
(ELIAS FISCHL STAT. CANCER HOSPITAL)

	NUMBER OF CASES*	NUMBER OF TERM PREGNANCIES†			
		0	1 TO 3	4 TO 7	8 OR MORE
Benign gynecologic conditions	230	9%	12%	27%	12%
Carcinoma of the cervix	117	12%	40%	35%	13%
Carcinoma of the endometrium	89	30%	36%	23%	0
Cystic mastitis and adenofibromas	109	22%	19%	21%	5%
Carcinoma of the breast	103	27%	42%	23%	8%

\*Only those cases with necessary data are included

†Abortions up to six months were not counted. Percentages rounded for clarity

of the cervix is greater than the number of single women, while the number of single women who die of cancer of the breast is greater than the number of married women or widows. An abnormally high proportion of patients with carcinoma of the cervix also have syphilis. This is also true of patients with carcinoma of the tongue but not of any other major form of cancer. Levin, in a special study of 930 patients with carcinoma of the cervix, found that 3.9 per cent of these had physical or serologic evidence of syphilis.

*Sarcomas* of the cervix are very rare. Piquand found only 68 in a series of 325 sarcomas of the uterus. They are more frequently found in patients 40 to 60 years old, but the rare "sarcoma botryoides" arises predominantly in infancy.

### Pathology

**Gross Pathology**—In the following order of frequency, carcinomas of the cervix arise from the posterior lip, the cervical canal, and the anterior lip. There are three distinct gross types of tumor, but these differences are not related to histologic variations.

*Ulcerating*—The ulcerating tumor is characterized by its infiltration and by loss of substance. As the cavity enlarges to destroy the cervix and to deepen into the body of the uterus, the centrifugal spread of the ulceration involves the vaginal fornices (Figs. 599 and 608).

*Exophytic*—This type of tumor may fill the entire upper half of the vagina without invading the fornices or parametria. These so-called "cauliflower" growths are accompanied by considerable secondary infection and spontaneous necrosis (Figs. 600 and 606).

*Nodular*—The nodular variation usually arises in the endocervix where the original ulceration is hidden. The tumor infiltrates through the submucosa and the entire cervical structure is replaced by a granulating mass. The spread to the vaginal walls is accompanied by a hard, nodular elevation of the mucosa at the borders of the ulceration. Finally there may be widespread ulceration (Figs. 601 and 605).

In their relentless progress, carcinomas of the cervix spread in three distinct directions: (1) to the fornices and vaginal wall, (2) to the body of the uterus, and (3) to the parametria. Secondly, they invade (4) the bladder, (5) the rectovaginal septum and rectum, (6) the vulva, and (7) the uterosacral ligaments. These events do not necessarily follow in chronological sequence. A

cases (4 per cent) were found in patients under 30 years of age. The incidence rises to a maximum in the 50-54-year age group.

It has been widely noticed that carcinoma of the cervix usually occurs in parous women (Table XLVIII). Bowing reported 1,481 cases of carcinoma of the cervix, only 8 per cent of which were found in single women. One or more pregnancies had occurred in 88 per cent of the patients. Based on these facts

## CARCINOMA of the CERVIX (453 cases)

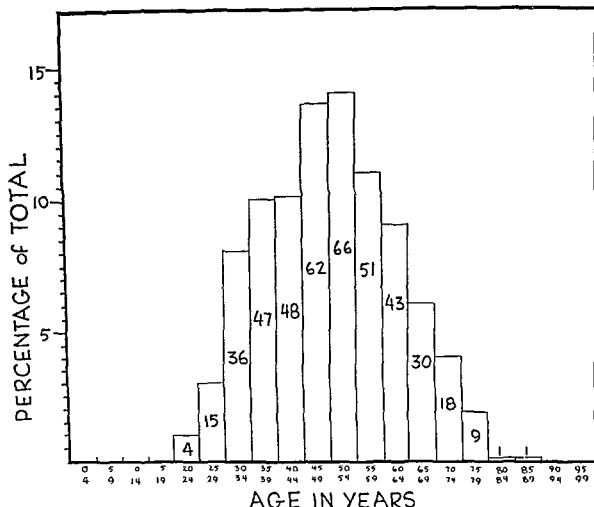


Fig. 590.—Age incidence of 453 patients with carcinomas of the cervix admitted to the Lilla Fischel State Cancer Hospital (1940-1946).

many authors have concluded that obstetrical trauma, lacerations, and improper care of tears were a local cause of cancer. It has also been suggested by Hofbauer that the repeated excessive stimulation of the uterine epithelium by the ovarian hormone may be an important factor in the production of cancer of the cervix in multiparous women.

Hurdon made a report based on the statistics of mortality for England and Wales showing that the number of married men and widows with carcinoma



and distorted by the tumor and because of this often the left ureter may be first distended and its lumen obstructed. It takes time, however, for the tumor to pierce the thick bladder muscle and to ulcerate the mucosa. The invasion of the bladder wall is accompanied by edema. The ureteral orifices may be practically occluded. Moreover, the tumor may grow around the terminal portion of the ureter and contribute to this occlusion. Actual invasion and ulceration



Fig. 591—Hydronephrosis and hydronephrosis due to compression of the ureters in the parametrium by carcinoma

relatively early carcinoma of the anterior lip of the cervix may invade the bladder before infiltrating the parametria and pelvic metastases may occur from early lesions still limited to the cervix, but this is rare

*Invasion of Fornices and Vaginal Wall*—The anterior fornix, much shallower than the others, is more easily but not as frequently invaded as are the lateral fornices. The posterior fornix is invaded by those tumors which have destroyed the posterior lip. Since this fornix is deep, its involvement is rarely an early occurrence. Once the vaginal wall is reached, the spread of tumor over it is accelerated. Besides invasion by contiguity, there may be retrograde permeation of the rich lymphatics of the vaginal mucosa. Isolated and sometimes pedunculated growths of the vaginal wall may be found at a distance from the primary tumor. From the anterior wall the tumor rapidly reaches the introitus. The distance to the posterior wall is greater, and consequently this is usually the last region to be affected.

*Invasion of the Body of the Uterus*—The thick uterine muscle is not often penetrated by carcinoma, but once the barrier of the isthmus has been passed the tumor may spread into the uterine cavity and enlarge the whole organ. In these rare instances the tumor remains for a long period of time within the muscular uterine frame, but it may eventually erode the serosa and even invade the neighboring intestine.

*Invasion of the Parametria*—Whether tumor breaks through the cervical muscle or whether it infiltrates out through lymphatic channels, once the surrounding areolar and subperitoneal tissue is reached, the tumor seems to develop easily and unhindered. This subperitoneal tissue is continuous with the one which fills the broad ligament, and it is toward the broad ligament that most carcinomas develop. The rich lymphatic network of the parametrium is perhaps responsible for this course. Within the parametrium the tumor grows without restraint. It grows around the ureter which traverses the parametrium behind the uterine artery and in its course to the bladder comes within 1.5 cm. of the cervix (Fig 588). Rarely is the ureter invaded, but tumor may involve the periureteral lymphatics and compress and occlude the ureter 2.5 cm. from the bladder. This results in hydronephrosis and hydroureters, which rarely may be bilateral (Fig 591). The tumor may develop in a nodular fashion which imitates but is not explained by the presence of nodes in the parametrium. In reaching the lateral wall of the pelvis the tumor finds its last barrier in the muscular fascia. Commonly the parametrium becomes larger and harder before tumor finally invades the wall.

Inflammatory changes in the parametrium almost invariably accompany the neoplastic invasion, but in the majority of cases, these changes are not remarkable. In some instances however the inflammation causes the parametrium to become diffusely indurated although not nodular.

*Invasion of the Bladder*—When the anterior lip of the cervix is involved, the tumor passes rather easily into the lax tissue which separates it from the bladder. The same is true when cervical ulceration has extended into the anterior fornix and vaginal wall (Fig 613). The bladder wall is at first displaced

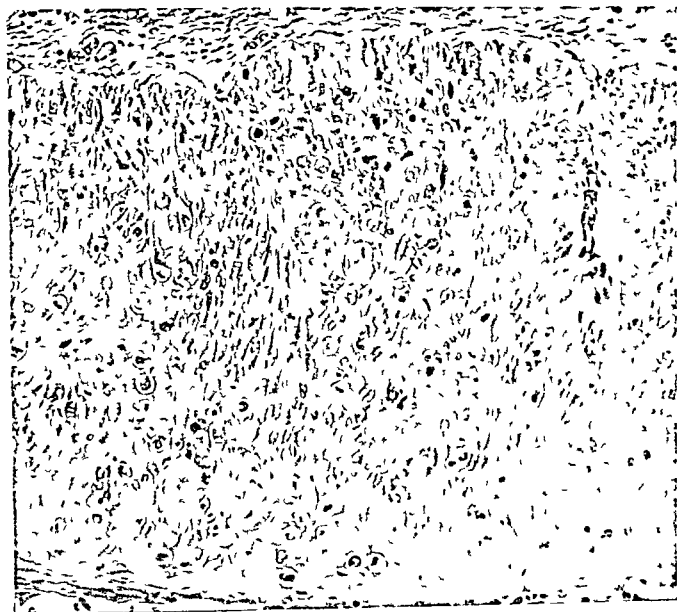


Fig 592 —Photomicrograph of a carcinoma of the cervix in situ in its preinvasive stage



Fig 593 —Epidermalization of cervical glands. This lesion occurs on the mucosa of polyps and should not be considered as carcinomatous degeneration

of the bladder mucosa are always accompanied by secondary infection and cystitis. With compression of the ureters and bladder invasion there are often dilatations of the ureters and pyelonephritis resulting in kidney failure. Infection of the kidney may be retrograde or hematogenous.

*Invasion of the Rectovaginal Septum and Rectum*—When tumor has invaded the posterior fornix and extended over the posterior vaginal wall, it may remain static there for some time. There, little by little tumor invades the muscular layer of the vagina and extends into the rectovaginal septum which becomes enlarged and indurated. The rectal mucosa is actually ulcerated only in advanced cases (Fig 612).

*Invasion of the Vulva*—The invasion of the lower third of the vaginal wall is sometimes accompanied by metastatic subcutaneous nodules in the thickness of the labia majora (Fig 610). The ulceration itself, however, may extend to the introitus and also invade the urethra.

*Invasion of the Uterosacral Ligaments*—Once the tumor breaks through the muscular frame of the cervix, it spreads easily into the fatty subperitoneal tissue which extends into the lower half of the large ligament to form the parametrium and into the uterosacral ligament. The lymphatics of this ligament are not as rich as those of the parametrium, and for this reason it is not as often invaded. It is only in advanced cases that the uterosacral ligament becomes rigid on one or both sides of the rectum. As a result there may be a constriction and later obstruction of the rectum (Pearson). The tumor may extend to the sacrum through this channel and directly invade that bone.

**METASTATIC SPREAD**—Through its copious lymphatic outlets the cervix may produce regional metastatic implants to the external iliac chain of nodes (pre-ureteral pedicle) or to the hypogastric nodes (retro-ureteral pedicle). Both of these lymphatic channels travel in the parametrium. Through the lymphatics in the uterosacral ligaments the tumor may establish its metastatic colonies in the sacral nodes and in the lumbar nodes of the promontory. Early lymphatic metastases take place only in very undifferentiated carcinomas. Distant blood-borne metastases from carcinoma of the cervix are not common. A substantial majority of the patients dying of carcinomas of the cervix present only pelvic spread of the tumor. The extension to the pelvic nodes, however, may be followed by invasion of the lumbo-aortic nodes and the cisterna chyli which drains all these nodes. From the cisterna chyli the tumor rapidly spreads to the thoracic duct, and as a consequence, left supraclavicular metastasis is found (Virehow, Troisier). Lung, liver, bone and brain metastases may be evident after the cisterna chyli and thoracic duct are invaded. Bone metastases nevertheless are comparatively rare, Laborde reported only fourteen cases of bone metastasis in a series of 1,743 carcinomas of the cervix treated at the Cancer Institute of Paris. The biologic characteristics of the tumor, seldom predictable on the biopsy slide, are the governing aspects of this spread.

**Microscopic Pathology**—The overwhelming majority of carcinomas of the cervix are epidermoid (or squamous cell). Even most of those which develop in the cervical canal where the mucous membrane is columnar in type are epi-

of infiltration except in one. Hysterectomies were performed, and a study of the whole specimen revealed unquestionable evidence of cancer in every case. We found carcinomatous changes limited to the surface epithelium in two cases and called them *carcinoma in situ* (Fig 592). Pund reported a routine study of 1,200 surgically removed cervixes in which forty-seven (3.9 per cent) early carcinomas in their preinvasive stage were found. The lesions appeared in the gland-bearing endocervical lining, probably from multipotent basal cells. It is generally accepted that such lesions may take several years before they become clinically evident. Epidermization of the cervical glands, often observed in polyps, should not be confused with carcinoma (Fig 593).

In general, the grading of epidermoid carcinomas is of little prognostic value. The degree of extension of the disease as expressed by their clinical stage is more important, but within a given stage, the establishment of a relative prognosis may be helped by the histologic grade. Epidermoid carcinomas Grade III, although more radiosensitive, are more prone to produce early metastases to the lymph nodes in the upper abdomen. Griconoff, in a thorough histologic study of a large number of cases, concluded that there was no histologic feature which could forewarn with certainty the possibility of metastases, but he found that a greater proliferative activity and a large number of mitoses were present in 42 per cent of his cases with distant metastases.

*Adenocarcinomas* of the cervix can, as a rule, be easily differentiated from epidermoid carcinomas. In some difficult instances silver staining may reveal a pattern of reticulum typical of the epidermoid group (Regaud, 1933). The distinction from adenocarcinomas of the endometrium invading the cervix may be more difficult. The typical adenocarcinoma of the cervix shows the characteristic tortuous cervical glands, and in many areas the resemblance to normal cervical epithelium can be recognized (Fig 594). Unlike those of the endometrium, adenocarcinomas of the cervix may produce mucin which can also be revealed by special stains. Adenocarcinomas of the ovary may also spread to the uterine fundus and to the cervix. They can be recognized by the secondary branching of the glands together with some clinical information.

*Sarcomas* frequently arise from pre-existing leiomyomas (Masson) and for this reason are rarely found in the cervix. The "sarcoma botryoides" of the cervix is formed by multiple, polypoid, vascular masses.

### Clinical Evolution

The onset of carcinomas of the cervix is seldom accompanied by alarming symptoms, and as a result the disease progresses into a moderately advanced stage before it is deemed worthy of investigation. Early carcinomas of the cervix (Stage I) make up only about 10 per cent of cases seen in the majority of clinics. In a good number of advanced cases the absence of symptoms or the apparent benignity of those present is the main cause of the late diagnosis.

**Early Symptoms**—The symptoms that could betray the existence of an early carcinoma of the cervix may give no concern to the patient during menstrual life. They are easily taken for inconsequential irregularities of a woman's physiologic burdens. An elongation of the menstrual period may be the only

TABLE XLIX HISTOPATHOLOGIC DISTRIBUTION OF 453 CASES OF CARCINOMA OF THE CERVIX IN PATIENTS ADMITTED TO THE ELIAS FISCHER STATE CANCER HOSPITAL DURING THE FIRST SIX YEARS OF ITS OPERATION

	CASES	PER CENT
Adenocarcinomas	17	3.7
Unclassified	8	1.7
Epidermoid carcinomas	429	94.5
In situ	2	.5
Grade I	15	3.5
Grade II	352	82.2
Grade III	46	10.7
Ungraded	13	3.0
Total	453	

dermoid carcinomas Table XLIX shows the histologic distribution of the 453 cases of carcinoma of the cervix in patients admitted for treatment to our hospital. The bulk of these cases are epidermoid carcinoma: Grade II and about 10 per cent are Grade III. Very few are differentiated Grade I carcinomas. We found the proportion of adenocarcinomas to be less than 4 per cent.

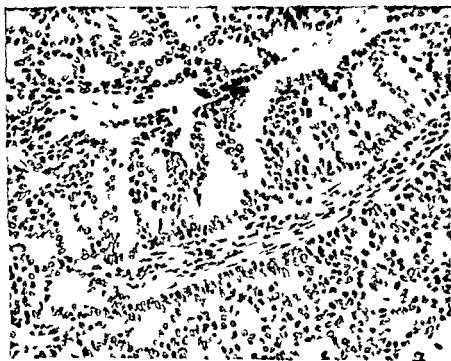


Fig. 94—Photomicrograph of a typical adenocarcinoma of the cervix. No resemblance to cervical glands.

Most carcinomas of the cervix can be easily diagnosed on microscopic examination. However, in early cases there may be a question as to what minimal histologic changes of the cervical epithelium justify a diagnosis of carcinoma. In this regard, errors may be made both by diagnosing carcinoma on minor benign changes as well as by failing to recognize actual early carcinomatous changes of the epithelium. Telande reported on a series of eleven patients in whom biopsy showed changes only in the surface epithelium without evidence

intense sacrococcygeal pain usually accompanies the production of a recto-vaginal fistula in advanced cases

The *urinary symptoms* are variable and inconstant. An early tumor of the cervix may cause some pollakiuria and even nycturia without actual invasion of the bladder. These symptoms result either from neighboring inflammation and hyperemia of the mucosa with a diminution of the bladder capacity or from an irritation of the urethra by the vaginal discharge. There may be a sensation of heaviness and some pain immediately following micturition, but these signs are only the result of mechanical displacement of the bladder. In contrast, an advanced tumor which has invaded the wall of the bladder and has produced extensive bullous edema may give minimal urinary symptoms. Hence, the degree of bladder invasion cannot be appreciated by relying on these symptoms. As a general rule, however, there is some degree of pollakiuria and nycturia associated with the invasion of the bladder wall by tumor.

When tumor has invaded the bladder and perforated its mucosa a *vesico-vaginal fistula* may form. However, the passage of urine through the vagina may be small and it may even pass unobserved or be considered merely as vaginal discharge. In other instances the urine passes through the fistula in one impulse, lasting only a few seconds.

*Constipation* is present only in advanced cases in which compression and reduction of the lumen of the large bowel has occurred. It is progressive and becomes very marked. *Diarrhea* may then develop as an automatic reaction of the bowel against a reduced bowel lumen. The passage of feces into the vagina through a *rectovaginal fistula* is rarely observed in spite of invasion of the rectal wall by tumor. The tumor growth usually obturates the area of destruction. However, when a slough of tumor does produce a fistula, the fecal material passes into the vaginal tube, causing both alarm and discomfort. As a general rule, however, a rectovaginal fistula forms only after treatment has melted the tumor.

*Nausea and vomiting* may be caused by upper abdominal metastasis. *Vomiting, convulsions* and finally *coma* may be due to uremia following compression of the ureters. *Anuresis* may be observed terminally.

Almost invariably, *weight loss* accompanies cancer of the cervix. The appreciation of it and the period of time over which it occurs are important. Lack of appetite is common. Whether the weight loss is the result of secondary infection, pain, and resulting inactivity, or drug consumption, the fact is that it may become marked (ten to thirty pounds). Secondary *anemia* is more or less severe according to the duration of the disease but is more acute with the hemorrhagic type of tumor. Repeated transfusions may have to be given during the first weeks of treatment. In spite of the almost constant secondary infection of these tumors, *fever* is observed only in rare cases. With fever, however, there may be evidence of a pyometrium or urinary infection. All these symptoms combine to give the patient a grave appearance which is further aggravated by analgesics and hypnotics.

sign for months. Hypomenorrhea and even amenorrhea are rarely observed. *Watery discharge*, slight but continuous, may also be present for months before it becomes blood stained. *Slight intermenstrual vaginal bleeding* may occur after coitus, exertion, or travel. Bleeding after coitus is usually startling enough to occasion an early examination. *Hemorrhage* is often the first symptom but it is seldom associated with early lesions. In general it accompanies rather advanced exophytic tumors which have developed rapidly and silently. *Yellow vaginal discharge* is rarely a first symptom, but occurs with the majority of cases in the later stages of the disease. *Pain* is very seldom the first symptom unless it is in the form of a lumbar or lower abdominal ache, such as is some times present preceding menstrual periods. The first symptoms produced by the tumor after menopause are usually distressing enough to instigate quick consultation, for vaginal bleeding and discharge are then unexpected. It is also true, however, that when this occurs two or three years after cessation of menstrual life, the patients sometimes believe that they are menstruating again and delay a medical interview.

**Late Symptoms**—In later stages of the disease the early symptoms acquire a different character and other symptoms gradually become associated.

A *yellow vaginal discharge* is present in the majority of advanced cases. It is characteristically foul smelling because of its high bacterial formation and carries with it, at times small fragments of necrotic tumor. This discharge is very irritating to the vaginal and vulvar mucous membrane and as a consequence, a variable degree of vaginitis and vulvitis may ensue. Abundant watery discharge is seldom encountered. *Vaginal bleeding* may appear only after sexual intercourse or marked exertion. In the majority of cases there is always some degree of bleeding, but it is usually associated with large, rapidly growing exophytic growths. Profuse continuous bleeding is exceptional. Death from hemorrhage may occur in these patients. Some cases present mild hemorrhages at intervals of weeks or months usually found to originate from craterlike growths which bleed as they invade a major vessel.

*Pain* is almost invariably present with carcinoma of the cervix and is a guiding sign in the diagnosis. A vague lumbar ache accompanies a majority of gynecologic conditions but in cancer of the cervix, the pain is progressive extending from the lumbar region to the hip, through the posterior or anterior aspect of the thigh, and stopping at the level of the knee. Later it extends to the ankle and toes. As a general rule, the greater the intensity and extension of the pain, the greater the pelvic involvement by the tumor. This pain is not easily explained. It is possibly a "reflex pain" resulting from a compression of the sympathetic nerves in the parametria. It may be unilateral or bilateral but is usually more intense and extensive on one side than on the other according to the extension of the disease. A suprapubic pain is symptomatic of invasion of the anterior vaginal wall or bladder. Moderate tenderness is some times present in one or the other iliac fossa but is seldom acute.

Pain which extends high in the dorso-lumbar region is usually due to compression of the ureters, hydronephrosis, and hydronephrosis. Epigastric pain is associated with involvement of the paravertebral nodes in terminal cases. An



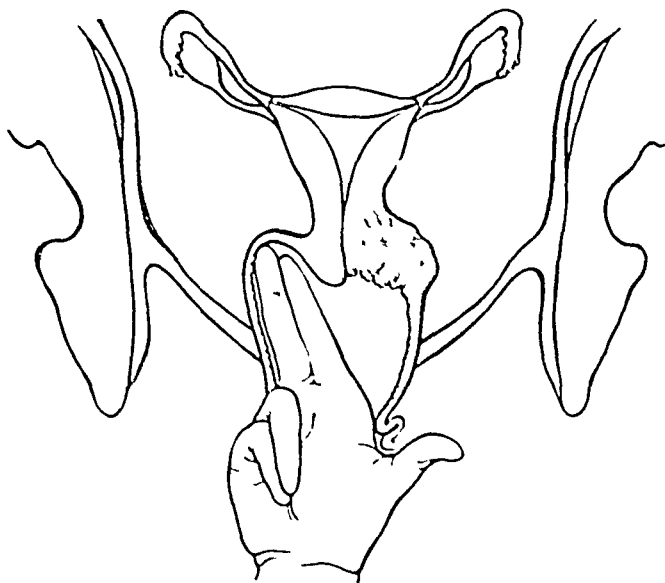


FIG. 595.—Vaginal palpation with two fingers of the right hand allows deep exploration of the cervix and the right fornix.

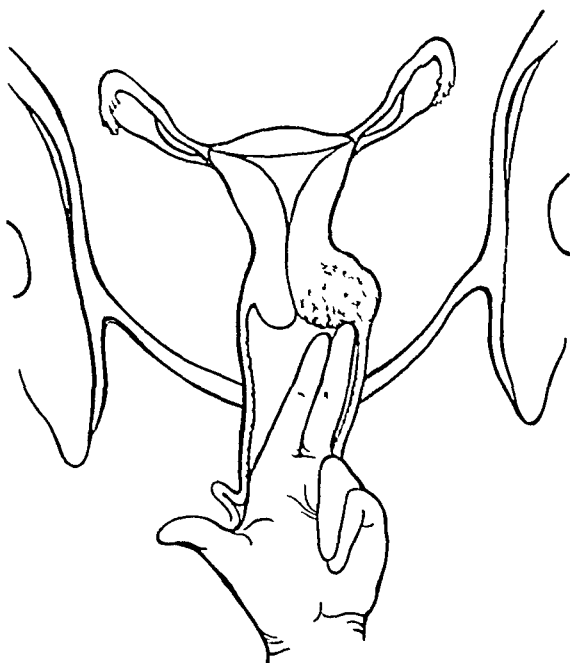


FIG. 596.—Vaginal examination with the left hand allows exploration of the left side. The lack of elasticity suggests parametrial extension but its limits cannot be definitely established by vaginal examination.

Patients not receiving treatment more often die of complications such as hemorrhage, toxemia, peritonitis, pyelonephritis, uremia, etc. Patients in whom treatment has failed frequently present a similar end due to local recurrence. But with better therapeutic techniques, a greater number of patients have been presenting distant metastasis after regional control of the disease. Gricouroff reported 242 cases of distant metastasis among 2,186 patients with carcinoma of the cervix treated at the Radium Institute of Paris, in 179 cases in which the approximate date of appearance was known, 130 occurred within three years, twenty others in the fourth and fifth years, and only twenty nine cases showed a metastasis after five years. Of these cases 113 presented no evidence of residual or recurrent carcinoma in the pelvis.

*Sarcomas* of the cervix develop very slowly. Sometimes they bleed profusely. Pain may become intense but it is usually a late symptom. Blood borne metastases to liver and lungs are not uncommon.

### Diagnosis

**Clinical Examination**—The extent of the disease or its curability are not necessarily indicated by the duration of symptoms or their intensity. Nor are the symptoms which accompany early carcinoma of the cervix pathognomonic of the disease for they may be present in chronic cervicitis, uterine myomas, cervical polyps, and a number of other nonmalignant conditions. The early diagnosis depends mainly on a detailed history, careful examination, and an intelligent evaluation of the findings.

A thorough and accurate recording of symptoms and their duration is an indispensable prerequisite to the examination of a patient suspected of having cancer of the cervix. Patients have a tendency to give the single complaint which appears most important to them such as vaginal bleeding, whereas a careful questioning will reveal that there was vaginal discharge for months before the bleeding started, that there was a lumbar pain which spread to the hip and later to the thigh on one side, or that micturition occurred several times in a night. All these details are of utmost importance.

The usual routine of gynecologic and obstetric examinations may not give enough information for a diagnosis, an evaluation of extension and staging of cancer of the cervix. Certain details of examination are herewith emphasized which are most satisfactory and have found the sanction of experience.

**Abdominal Palpation**—Before the gynecologic examination is started a careful palpation of the abdomen must be done, for a voluminous, easily palpable lower abdominal mass can be missed. Palpation of the iliac fossae may disclose the presence of a metastatic mass which usually arises laterally from behind the Poupart's ligament. If a mass is not present, this palpation may reveal tenderness on the side of greater extension of the tumor. This examination should also include the inguinal regions for detection of adenopathy.

**Vaginal Inspection**—It is customary and safer to start a gynecologic examination by a bimanual palpation and most gynecologists insist that this be done before a speculum is introduced in the vagina. However manipulation causes most tumors to bleed to such an extent that direct inspection through

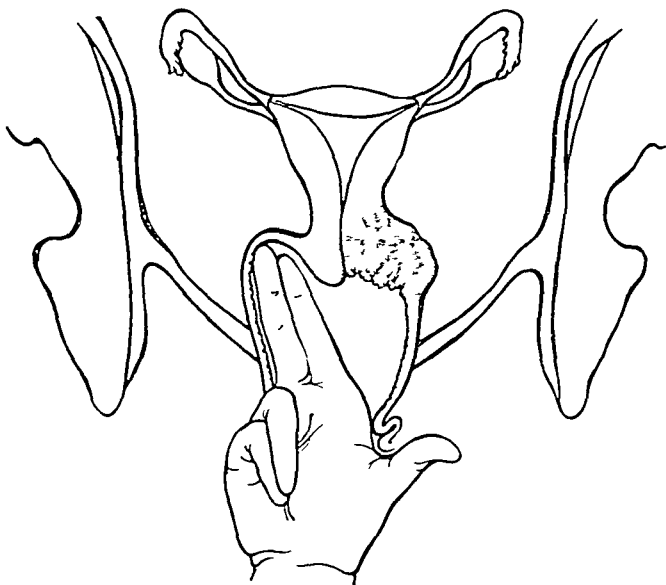


Fig 595 --Vaginal palpation with two fingers of the right hand allows deep exploration of the cervix and the right fornix

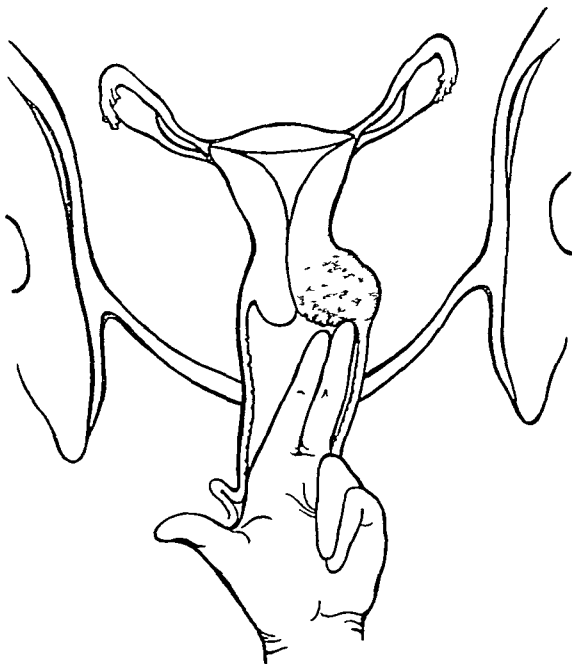


Fig 596 --Vaginal examination with the left hand allows exploration of the left side. The lack of elasticity suggests parametrial extension but its limits cannot be definitely established by vaginal examination



Fig 597—Rectal palpation with the right index finger allows complete exploration of the right parametrium. When the finger can be introduced between the tumor mass and the pelvic wall the parametrium is probably not totally invaded.

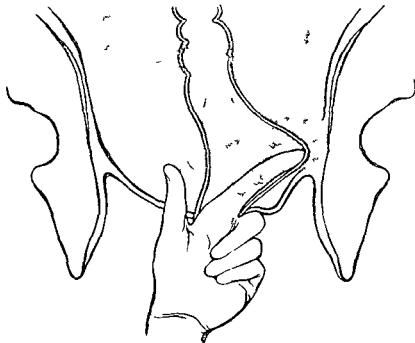


Fig 598—Rectal palpation with the left index finger allows complete exploration of the left parametrium. When the tumor mass is continuous with the pelvic wall and there is no notch between the tumor and the pelvic wall the clinical assumption is that the tumor has already invaded the pelvic wall.

the speculum is hampered, and the investigation is, of necessity, hurried. In the practice of cancerology, it is therefore more convenient to start with the speculum examination following a mere exploration of the vagina with the gloved finger of one hand. In this way the examiner may have a direct view of the tumor before it bleeds.

The *colposcope* of Henselmann has been recommended as a means of diagnosing early lesions of the cervix by direct examination. In a darkened room this instrument allows a magnified view of the cervix through the speculum. By painting the cervix with an iodine solution (Gram's), the normal mucosa becomes brown while areas of abnormal epithelium remain uncolored. At best, however, this procedure merely indicates the area where a biopsy should be taken.

*Vaginal Palpation*—With a cancer of the cervix, a vaginal palpation furnishes information as to the consistency of the cervix, the depth of all vaginal fornices, the size and position and mobility of the uterus, and the possible extension of induration to the vaginal walls. This information cannot be accurately obtained unless the examiner with gloves on both hands, does two bimanual examinations, one with the right hand in the vagina and left hand above the symphysis pubis, and the other with the hands in a reverse position. The index and middle fingers of one hand must reach far into the lateral fornix in order to feel the induration of the mucosa or the diminution in depth of the fornix (Figs. 595 and 596). The same hand cannot reach equally deep into both fornices. The rotation of the hand is only an unsatisfactory maneuver that confuses the appreciation and comparison of the findings in the two sides.

When the tumor extends over the posterior fornix and wall, another type of bimanual examination is necessary. With the fingers of one hand placed in the vagina, palm facing down, and the index finger of the other hand introduced in the rectum, palm upward, the operator will be able to establish whether the invasion of the mucosa is superficial or if the tumor has invaded the recto-vaginal septum.

*Rectal Palpation*—The rectal examination establishes the extent of the parametrial infiltration, where the vaginal palpation only gives a suspicion of it. The diminution in depth of a lateral fornix and loss of its elasticity and depressibility as felt via the vagina can be taken as signs that the tumor has broken out of the cervix and extended into the areolar tissue of the parametrium but it cannot substantiate by itself how far out the tumor has spread.

Palpation via the rectum is limited to the use of either the index or the middle finger. With the right hand the examiner can palpate the posterior surface of the right parametrium in its entire length to reach the pelvic wall on that side (Fig. 597). The use of the same right hand finger for exploration of the left parametrium is unsatisfactory. The left index or middle finger should be used to explore the left half of the pelvis (Fig. 598). The parametria are normally elastic and soft, but in some patients, particularly those with a history of pelvic inflammatory conditions, the parametria may have become fibrotic and give a false impression of invasion by the tumor. These postinflammatory parametria are usually smooth, cordlike bands conserving some elasticity without

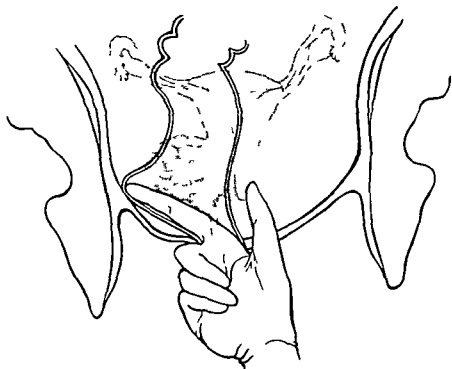


Fig 597—Rectal palpation with the right index finger allows complete exploration of the right parametrium. When the finger can be introduced between the tumor mass and the pelvic wall the parametrium is probably not totally invaded.

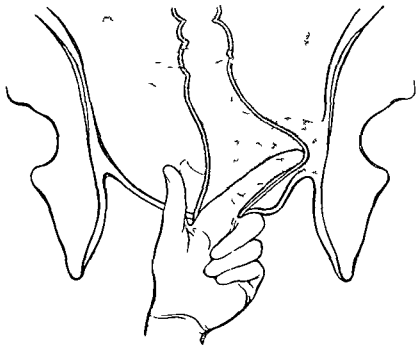


Fig 598—Rectal palpation with the left index finger allows complete exploration of the left parametrium. When the tumor mass is continuous with the pelvic wall and there is no notch between the tumor and the pelvic wall the clinical assumption is that the tumor has already invaded the pelvic wall.

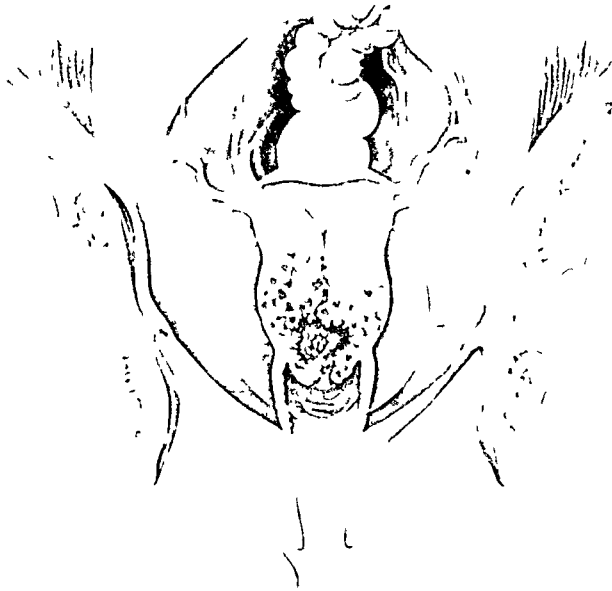


Fig 604

Fig 603 —Stage II carcinoma of the endocervix with invasion of the uterine corpus  
 Fig 604 —Stage II carcinoma of the cervix with early invasion of the fornix

increase in volume. Once a patient has received radiotherapy, the parametria may become entirely normal to palpation, but the appreciation of residual tumor in the parametria or the diagnosis of parametrial recurrence necessitates in most cases, the support of symptoms such as pain, and repeated follow up examinations. Patients who have been heavily irradiated may have diffuse pelvic edema sometimes associated with minor postirradiation effect of the bowel. One should be cautious in diagnosing such bilateral indurations of the parametria as recurrences.

**Clinical Classification**—When panhysterectomy was the accepted treatment for carcinomas of the cervix, these tumors were classified according to their eligibility for this therapy. An analysis of 1,574 cases of carcinoma of the cervix published by Healy in 1931 gave the following results:

Early (operable)	12.5 per cent
Borderline	12.5 per cent
Advanced	75 per cent

This classification was then justifiable because the most important factor in the prognosis was the operability of the patient. The concept of operability, however, is a technical one. A relatively early carcinoma, having invaded the vaginal wall, may be inoperable and therefore labeled "advanced."

In 1929 the Subcommittee on Radiotherapy of Cancer of the Committee on Hygiene of the League of Nations contributed a clinical classification of carcinomas of the cervix in four stages. This classification has established a basis for prognosis through the careful clinical evaluation of the cases. To avoid confusion we shall give details only of the revised version of this classification (Heyman). Mobility and fixation of the uterus were eliminated as factors in the 1937 revision of the classification and thus an item of too much personal appreciation was discarded. The new definitions have, for the most part, affected the allocation of carcinomas between Stage III and Stage IV. As it stands today, the *League of Nations* classification can easily be utilized by the inexperienced examiner having only a short training. It is most important, however, to follow the discipline in the technique of examination which is outlined above.

The following general rules should be adhered to in order to make classifications which will stand fair comparison:

(1) *Allocation in stages should be made before starting treatment and remain.* Allocation should be postponed only pending a special examination like cystoscopy which, in turn, should be performed prior to treatment.

(2) *The general condition of the patient is not a factor in the classification.* A patient in uremia may only be a Stage II. Hopeless cases are not necessarily Stage IV.

(3) *Neither mobility nor fixation of the uterus or tumor is a factor in the allocation.* Mobility and fixation were deciding elements in the classification of 1929 but have now been eliminated.

(4) *When in doubt as to the allocation of a case between two stages, the earlier stage should be chosen.* It is sometimes difficult to estimate whether the





Pl. 698

Fig. 697—Stage III carcinoma of the cervix. The tumor has invaded the lower third of vagina.

Fig. 698—Stage III carcinoma of the cervix. Cervical ulceration with invasion of both sides in their entire length. The total invasion of one or both parametria requires radical hysterectomy at this stage.

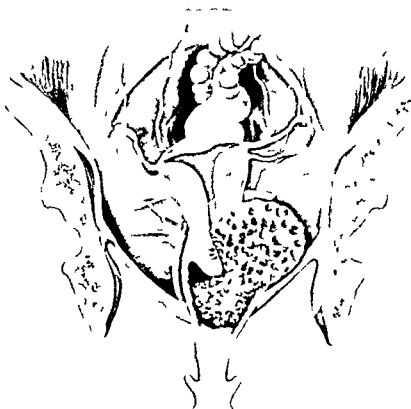


Fig 606

Fig 60 —Stage II carcinoma of the cervix Nodular tumor with invasion of the fornix and the adjacent part of the parametrium

Fig 606.—Stage II carcinoma of the cervix  
fornix and almost the entire left parametrium

with with invasion of the  
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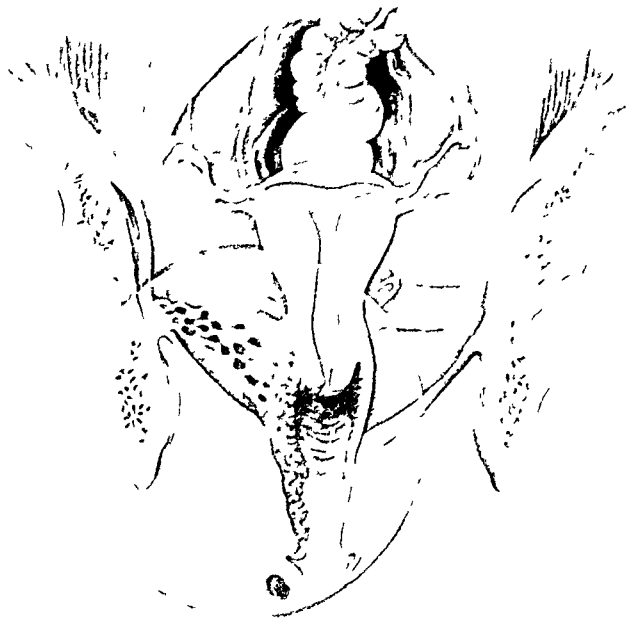
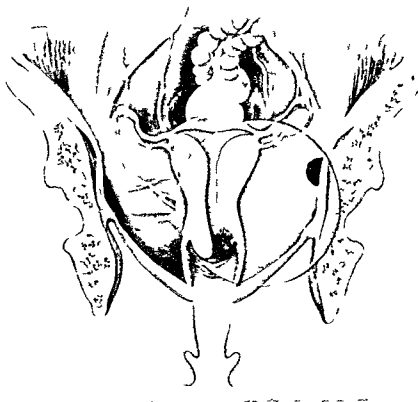
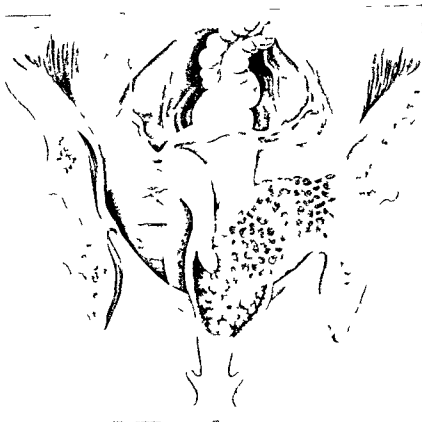


Fig. 611

Fig. 610—Stage IV carcinoma of the cervix. The tumor has extended to the internal os and there is a metastatic nodule within the labium majus.

Fig. 611—Stage IV carcinoma of the cervix. The tumor has already metastasized to the external iliac nodes and there are large palpable masses above the anatomic limits of the pelvis.



B

Fig. 609—4 Stage III carcinoma of the cervix exophytic tumor occupying the upper half of the vagina and extending to the entire left parametrium.

B Stage III carcinoma of the cervix. A small lesion which has already metastasized. The metastatic nodule can be felt against the pelvic wall on rectal palpation.

lower third of the vagina is invaded or whether a parametrium is entirely involved. Doubtful cases should be placed in the earlier stage (Stage II) instead of in the later stage (Stage III).

(5) *The presence, in the same case, of two or more conditions characterizing a stage does not affect the staging.* Thus, theoretically, there may be a complete invasion of the entire upper two-thirds of the vagina, of the body of the uterus, and of most of both parametria and the case still be a Stage II.

(6) *If possible, the difference should be noted between neoplastic and inflammatory infiltration of the parametrium.* This applies, for instance, when there has been a spontaneous regression of the tumor between two examinations before the institution of radiotherapy.

(7) *Previously treated cases should be grouped separately, for the appreciation of the extent of recurrences is considerably more difficult than in untreated cases.* The prognosis is usually rather poor just by virtue of previous treatment, regardless of the extension of the disease.

The following condensed definitions will facilitate classification of the majority of cases.

**Stage I**—*Irrespective of size, character, or secondary infection, the tumor is strictly confined to the cervix.* Whether the tumor is limited to one lip or has involved the entire cervix and increased its diameter, it should be considered a Stage I if there is no evidence of involvement of the fornices, of the parametria, or of the body of the uterus (Figs 599 to 602).

### Stage II—

*Parametrium.* The tumor infiltrates the parametrium on one or both sides but does not reach the pelvic wall (Fig 605). On rectal palpation, the finger finds a space between the tumor and the pelvic wall (Fig 597).

*Vagina.* The tumor invades the vaginal wall but does not involve its lower third (Fig 604). It must not be forgotten that the anterior vaginal wall is much shorter than the posterior wall and as a consequence the division of the vaginal walls in thirds cannot be expressed in units of measurement but is only a clinical estimate. Also belonging in this group are those cases which have isolated implants or metastatic growth in the upper two-thirds of the vaginal mucosa from a relatively early carcinoma of the cervix.

*Corpus.* Tumor spreads to the body of the uterus through the endocervical canal (Fig 603). This is sometimes difficult of appreciation, for the uterus may be enlarged because of the presence of the pyometrium and not because of actual invasion of the body of the uterus. A coexistent uterine myoma may likewise give the impression that the uterus has been invaded by the tumor. A curettage of the endometrium may be of value in some of these cases.

### Stage III—

*Parametrium.* The tumor invades the parametrium in its entire length on one or both sides (Fig 608). On rectal palpation the examiner will be unable to place his finger between the tumor and the pelvic wall (Fig 598). In most cases, invasion of the wall is accompanied by an expansion of the parametrium as it approaches the pelvic wall.

Fig 612

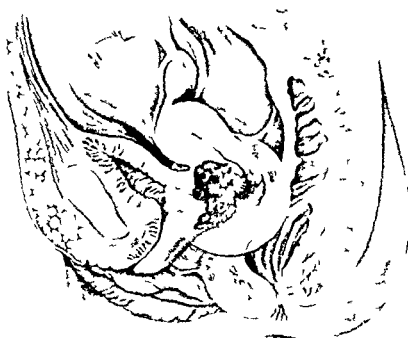
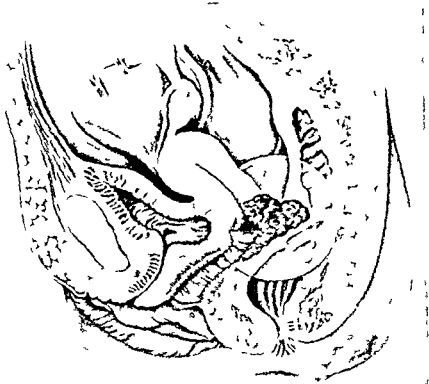


Fig 613

Fig 612—Stage IV carcinoma of the cervix. The tumor has invaded the posterior vaginal wall and rectovaginal septum. Bimanual vaginal and rectal palpation reveals evidence of invasion within the septum.

Fig 613—Stage IV carcinoma of the cervix. The tumor has invaded the anterior fornix vaginal wall and wall of the bladder. The staging is only possible after cystoscopy which reveals bullous edema of the trigone area.

This, however, does not imply actual invasion of the bladder wall, the factor with which we are concerned. Furthermore, invasion of the bladder wall does not necessarily mean invasion of the bladder mucosa, since there may be extensive invasion of the bladder without actual perforation into its lumen. The clinical symptoms are very misleading in this respect. Some cases with an extensive involvement of the bladder wall have no urinary symptoms, while others with external deformity but no actual invasion may have pollakiuria and nycturia.

A routine cystoscopic examination of *all* cases of carcinoma of the cervix is indicated. Although this examination is generally done only when there is a question of bladder invasion, the study of bladder changes which accompany the earlier stages of carcinoma of the cervix is of value.

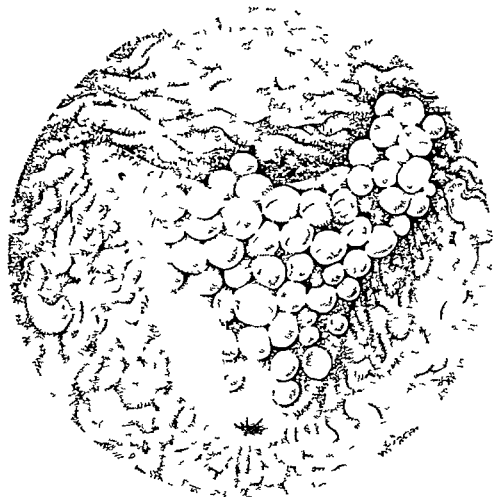


Fig. 614—Sketch of a typical bullous edema of the trigone area of the bladder. This finding on cystoscopic examination can be taken as a certain sign that the bladder wall has been invaded by the tumor.

A cystoscopic examination often reveals an extensive deformity of the trigone area, a finding seen even in Stage I carcinomas of the cervix. This mass may become bulky and compress the posterior bladder wall. Small areas of congestion of the trigone, ecchymosis, and even cystitis may be discovered. There may be exaggeration of the rugae of the floor of the bladder but none of these findings imply an actual invasion of the bladder wall. Only the presence of *bullous edema* of the trigone area (Fig. 614) with its characteristic grapelike appearance of unequal edematous semitransparent bullae can concede the cystoscopic diagnosis of bladder wall invasion. Of course, the tumor may have already ruptured into the mucosa, areas of ulceration may have developed, and vesicovaginal fistulas may already be present, but these are self-evident signs of bladder invasion.

The cystoscopic examination should always be augmented by the study of the ureteral meatus by means of an intravenously injected dye. When tumor com-

*Vagina* The tumor invades the vaginal wall down to its lower third (Fig 607) Also belonging in this stage are those cases which have an isolated implant or a metastatic growth in the lower third of the vaginal mucosa

*Isolated pelvic metastasis* Irrespective of the extent of the primary growth, isolated metastasis against the pelvic wall is present (Fig 608) Pelvic lymph node metastasis may be felt on rectal palpation as hemispherical masses attached to the pelvic wall on its posterolateral aspect This instance emphasizes the necessity of a thorough examination even in the earliest cases

#### Stage IV —

*Bladder* The tumor invades the bladder wall (Fig 613) The presence of a vesicovaginal fistula is an obvious sign, as is a positive biopsy obtained through the cystoscope The presence of frank bullous edema (Fig 614) may be taken as a certain sign of invasion of the bladder wall by the tumor Extrinsic deformity of the trigone area of the bladder, hyperemia, and linear edema may be observed in very early cases but these are not signs of bladder invasion

*Rectum* The tumor invades the rectovaginal septum (Fig 612) On combined rectal and vaginal palpation the septum is found enlarged and indurated and the rectal wall is indurated and fixed The rectal mucosa need not be ulcerated the appreciation of tumor extending into the rectovaginal septum is sufficient A rectovaginal fistula is an obvious sign of rectal invasion

*Extrapelvic* Tumor extends above or below the limits of the true pelvis (Figs 610 and 611) The ulceration of the vaginal wall has extended to the vulva or there are palpable nodules in the thickness of the labia majora The presence of abdominal or inguinal metastasis also places the case in this stage

*Distant metastases* Irrespective of the extent of the primary growth, distant metastases are present Upper abdominal left supraclavicular lymph, liver, lung, or brain metastases may be found but seldom in cases which are not locally advanced

It must be remembered that these four stages are a clinical classification and that even in the most expert hands a case allocated according to the preceding rules could eventually prove to have been more extensive than estimated or vice versa In spite of this possibility, the classification is good and at present has no valuable substitute The degree of extension of carcinomas of the cervix is not always parallel with the duration of symptoms The clinical classification also takes into consideration the therapeutic possibilities in each group and constitutes the best available single factor in the establishment of a prognosis

Other classifications such as the one proposed by Schmitz have a greater emphasis on the subdivision of early cases and a tendency to assemble the advanced ones

#### Special Examinations —

*Cystoscopy*—One of the most delicate factors in the classification of carcinomas of the cervix is the diagnosis of bladder invasion as demonstrated by cystoscopy As it has been said in the foregoing carcinoma of the cervix often spreads forward into the adipose tissue which separates it from the bladder



**Biopsy**—Obtaining a satisfactory specimen for microscopic examination may be the most important step in the diagnosis. A prerequisite of a good biopsy specimen is a good forceps which should procure the tissue by cutting, not merely by grasping, it off. The French gynecologist, Jean Louis Faure, devised a very sturdy biopsy forceps which furnishes a large specimen (Fig 615). The instrument is curved, allowing a view of the exact site from which the specimen is to be taken.

The biopsy specimen should be taken from the border of the lesion and as near as possible to the normal tissue. Large fragments taken from the center of an exophytic growth are composed mainly of necrotic tissue and do not always allow a pathologic diagnosis of carcinoma. A biopsy from the cervical canal can be obtained only by curettage, which requires greater care and often anesthesia. In these cases it is preferable to hospitalize the patient and to perform a dilatation and curettage under spinal anesthesia.

The diagnosis of carcinoma of the cervix by microscopic examination of vaginal smears (Papanicolaou) has shown unquestionable accuracy. The procedure, however, is not indicated in the overwhelming majority of cases of carcinoma of the cervix where the tumor is clinically evident and the biopsy becomes only a means of assuring a pathologic diagnosis. When the diagnosis is in doubt, a study of cervical and vaginal smears may be of additional value in the diagnosis. The procedure, however, requires long study of several specimens by a specially trained pathologist, and although a high percentage of accurate diagnoses can be thus obtained, the procedure cannot compete with the standard methods such as biopsy of the cervix and dilatation and curettage of the endocervix. In prophylactic survey of nonsymptomatic women in which biopsy and curettage would not be justified, the examination of vaginal smears may contribute (although at the expense of valuable time and effort) a few early diagnoses of cancer of the uterus.

**Differential Diagnosis**—Early carcinoma of the cervix may present itself in any of the following clinical forms:

*Ulcerating*—This is usually an irregular ulceration with a necrotic center surrounding the os. The evolution is toward a crater.

*Exophytic*—At a very early stage, the cervix around the os may have a granular appearance which is sometimes also present in chronic cervicitis, but in the latter the tissue is not friable. These granular areas rapidly rise and become soft, friable, pedunculated growths which bleed easily.

*Nodular*—Usually there is a hidden ulceration in the cervical canal. The cervix becomes enlarged, indurated, and irregular. The mucous membranes may be intact. Bleeding appears from the os.

In its very early stages carcinoma of the *endocervical canal* is compatible with a cervix of normal size and consistency which rapidly extends to the vagina. The diagnosis of moderately advanced lesions is obvious, but early lesions may be confused with numerous other entities.

*Sarcoma* of the cervix is usually a grapelike polypoid mass with great tendency to bleed and a very hard consistency. If this is observed in a child, the diagnosis of sarcoma should be strongly considered.

presses the ureter at the site of its termination in the bladder, the urine output on this side is either noticeably diminished or entirely absent. In this case the meatus becomes punctiform and may be surrounded by edema. Probing of the ureters may be done to investigate a possible obstruction. Aman Jean described a peculiar distortion of the bladder toward the left which he found to be progressively marked as the tumor advanced. The right meatus changes from its normal position (7 30 o'clock) toward the lower midline (6 o'clock), while the left meatus deviates from its normal position (4 30 o'clock) toward a lateral position (3 o'clock).

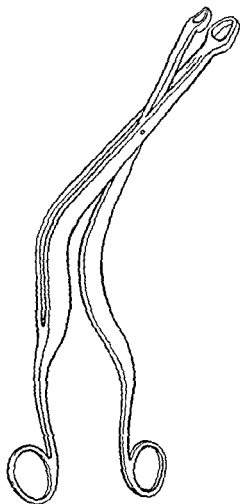


Fig 515—Curved biopsy forceps with sharp cutting edges designed by Faure for the purpose of removing specimens from nodular tumors of the cervix.

**Pyelograms**—Although carcinoma of the cervix may have repercussions on the urinary system, it must not be forgotten that many adult females, particularly the multiparas have abnormalities of the urinary system. On the other hand the existence of hydronephrosis and hydroureter due to cancer is not always clinically discernible and for this reason a routine intravenous pyelography, complementing the cystoscopic findings, may be of great value. Only when there is already a compression of the ureters and the serum non protein nitrogen is elevated is a retrograde pyelogram indicated.





# PLATE VIII

Cervical erosion

Eversion of the cervix with chronic cervicitis

Benign polyp of the cervix

Early carcinoma on a lacerated cervix

(Courtesy of Dr B Z Cashman Department of Gynecology School of Medicine University of Pittsburgh and the Elizabeth Steel Magee Hospital Pittsburgh Pa )

of prominent surgeons (Freund, Ries, Clark, Kelly), the technique for a radical hysterectomy was perfected about fifty years ago. This operation was practiced on a large scale by Wertheim, of Vienna, whose name was given to the operation because of his thorough study of clinical material, his painstaking pathologic research, and conscientious follow-up of patients. In the beginning, the operation was applied to a rather large proportion of the cases. The broadening of the concept of operability to its maximum limits was then justified, as surgery was the only hope of recovery. Experience brought about the necessity of limiting its indications to a smaller but worth-while group of cases in which the operation was not only technically possible, but also therapeutically successful. With the development of radiotherapeutic methods following the discovery of ionizing radiations, it was soon admitted that the Wertheim operation had met an early and powerful competitor, and, although surgery was never entirely abandoned, it was practiced very sporadically for many years.

The radical hysterectomy, nevertheless, remains a powerful therapeutic agent in the treatment of early carcinoma of the cervix. The main disadvantages of this operation are its high operative mortality and its morbidity rate. The recent improvements in anesthesia, the increasing understanding of shock and its prevention, and the improved control of infections have resulted in a diminution of the operative mortality and have justified a rebirth of enthusiasm for the surgical treatment of carcinoma of the cervix. Emmert reported an operative mortality of 14 per cent. Meigs claims an almost negligible operative mortality while pointing to a persistent high incidence (10 per cent) of injury to the ureter. But the unquestionable good results of the Wertheim operation done by skillful hands are no better than those of equally skillful radiotherapy. In comparing the results of surgery and radiotherapy in early carcinomas of the cervix, an important point is often forgotten. A surgeon who undertakes the operation of an assumed Stage I may find the tumor to be more locally extensive than estimated or may discover metastatic lymph nodes. These cases are not then included in the statistics of results since they are obviously not early carcinomas. But when the radiotherapist undertakes the treatment of a carcinoma of the cervix Stage I, he, too, may be treating a patient with a larger lesion than suspected or one with metastases, but his case will be included in the statistics of final results.

An important factor in the choice of treatment must be the skill with which it is to be applied. Furthermore, the sense of proportion in this controversy of radiotherapy versus surgery in the treatment of operable carcinomas of the cervix must not be lost, for the number of cases suitable for treatment constitutes only 10 per cent of the total number of patients who apply for treatment in the average clinic (Table L). It has been suggested that surgery be reserved for the treatment of early carcinomas in young women in order to preserve them from an early artificial menopause. This is perhaps justified, but of 453 cases seen in our hospital, only 55 were in women less than 35 years old, and only 10 per cent of these had Stage I lesions. Radiotherapeutic tests as a means of deciding on the treatment that is indicated are not justified. The choice of surgical treatment because of alleged radioresistance of the tumor has

**Benign Cervical Ulcerations**—Ulcerations of the cervix are usually large areas of superficial erosion around the os. They may be observed in cases of vaginitis or may be due to trauma caused by pessary or some other foreign body. Nonmalignant ulcerations are usually superficial and multiple and are not indurated (Plate VIII)

**Syphilis of the Cervix**—Chancres of the cervix are rarely found. They are usually situated on the anterior lip and look like a clear cut ulceration about 1 cm. in diameter. The base is indurated and there is little bleeding. Chancres may be found on a cervical erosion and circle around the os. Carefully taken specimens will reveal the *Treponema pallidum* in microscopic dark field examination. Secondary syphilis is quite often accompanied by superficial wide ulcerations of the cervix which are covered by yellowish false membranes. In these cases there are usually other manifestations of the disease and the serum Wassermann or Kahn tests show a positive reaction. *Leucoplakia* of the cervix is most often a secondary syphilitic manifestation. It may be considered as precancerous. Tertiary syphilis of the cervix in the form of a gumma is seldom observed.

**Tuberculosis of the Cervix**—Tuberculous lesions of the cervix are mostly secondary, and consequently the diagnosis is facilitated by locating other indications of the disease in the lungs or bladder. These cases are usually confused with carcinoma, but tuberculous lesions of the cervix, whether ulcerative or proliferative, are accompanied by considerable secondary infection, and pyometra and endometritis may be present as well as tuberculous lesions of the endometrium and Fallopian tubes. Multiple tuberculous lesions are easily recognized, but in the proliferative type the diagnosis is only possible with biopsy.

**Cervical Polyps**—Cervical polyps produce a scanty, spotty type of bleeding, the tumor is generally small pedunculated, and nonulcerated and protrudes from the os (Plate VIII). It may be accompanied by a more or less important degree of inflammation. In some instances the polyp may break down and become necrotic, and thus be confused with carcinoma. Mezer reported a study of 1,639 cervical polyps among which only five degenerated into carcinoma. Cervical polyps are as a rule easily removed by grasping and twisting with a forceps. This will provide sufficient material for pathologic study.

**Chronic Cervicitis**—Chronic cervicitis may offer great difficulty in differential diagnosis with an early carcinoma. In general, chronic cervicitis occurs in a younger group than does carcinoma. The cervix is enlarged and indurated and presents a marked granulation around the os. Bleeding is usually scanty, postcoitus. Cervical erosions may be associated and also some degree of pelvic inflammation. In removing a specimen for biopsy, the tissues are found fibrotic rather than friable. Negative biopsies should be complemented by dilatation and curettage to assure that a carcinoma is not present.

### Treatment

**SURGERY**—Near the end of the nineteenth century, only patients with carcinomas of the cervix which could be entirely eradicated by means of vaginal excisions or cauterizations had a chance of being cured. Thanks to the efforts



cussion between Regaud and Faure at the French Academy of Medicine, which became the turning point for a wide acceptance of radiotherapy as the treatment of choice

Regaud, Coutard, and Lacassagne, working at the Radium Institute of the University of Paris, brought to light a new technique of radiumtherapy which emphasized protraction in time and, most important, the necessity of adjunctive external roentgentherapy

The techniques of curietherapy were first investigated and the knowledge rapidly and widely disseminated. The particular features of the handling of curietherapy were studied and made equally available to the surgeon, gynecologist, and radiotherapist. This has been the cause of the emphasis which is still put on the intracavitary treatment of carcinoma of the cervix. *But if the internal irradiation can be called the most important single factor in the treatment of early cases, a thorough external roentgentherapy is the most important single factor in the treatment of advanced cases* (Regato).

Regaud demonstrated that when radium alone was applied to all stages of carcinoma of the cervix, the percentage of cures rapidly decreased with the advanced stages, while treatment with combined roentgentherapy and curietherapy contributed commendable results in the advanced group (Table LI).

TABLE LI THE VALUE OF EXTERNAL PELVIC ROENTGENTHERAPY IN TREATMENT OF CARCINOMA OF CERVIX

(Data from Regaud, Radium Institute of the University of Paris)

	INTRACAVITARY CURIETHERAPY ALONE (1919-1929)			INTERNAL ROENTGENTHERAPY PLUS CURIETHERAPY (1926-1940)		
	CASES	WENT 5 YRS.	PERCENTAGE	CASES	WENT 5 YRS.	PERCENTAGE
Stage II	173	51	31	217	100	46
Stage III	133	10	7	226	77	31
Stage IV	---	--	--	24	2	8

*External Pelvic Roentgentherapy*—It is the custom of some clinics to start treatment of early cases with intracavitary application of radium followed by external irradiation. We believe that *a thorough external irradiation of the pelvis is an important first step in the treatment of all cases*. The institution of external pelvic irradiation as a preliminary step has several definite advantages. Secondary infection and inflammation which accompany the tumor are greatly reduced. The pain, if it was present, disappears, the patients become euphoric, and their general condition improves. Moreover, the physical dimensions of the tumor are reduced to boundaries within which their sterilization is possible by internal irradiation. It is true that as a consequence of the shrinkage of the tumor and vaginal fornices after external roentgentherapy, the intracavitary application of radium may be rendered more difficult, but this is overbalanced by the advantages previously mentioned.

External irradiation alone may reach the entire tumor area in sufficient quantities to sterilize the tumor without help of further internal irradiation. Baclesse reported on a series of forty-five patients with Stage III and Stage IV carcinoma receiving external pelvic roentgentherapy alone, seven of whom (15

TABLE I. ISOLATION OF CASES IN DIFFERENT STAGES OF CARCINOMA OF CERVIX CLASSIFICATION OF 1929 BEFORE ITS REVISION IN 1937  
(Data from Heyman, J Acta obst & gynec Scandinav, 1938)

	CASES	PERCENTAGE
Stage I	607	11
Stage II	1 625	29
Stage III	2 417	42
Stage IV	1 020	18
Total	5 669	100

Cases reported by nine institutions 898 other cases neither staged nor treated mostly advanced cases are not included

no factual basis. No carcinoma arising from the cervix is radiosistant. Even adenocarcinomas, which for many years were judged less amenable to radiotherapy, have long been recognized as radiosensitive and radiocurable.

Attempts have been made to combine irradiation and surgical treatment in carcinomas of the cervix. Leveuf advocated a dissection of the "principal" chain of lymphatics of the cervix. This is by no means a complete dissection of all lymphatics and their corresponding nodes. Taussig applied this operation, which he called *iliac lymphadenectomy*, to the treatment of patients with Stage II lesions after external irradiation had been completed and before intracavitary radiumtherapy was instituted. Of seventy patients so treated, forty six showed no node metastases. All that can be said is that in these forty six patients the operation was useless. Of the twenty four who presented lymph node metastases, only five (21 per cent) were well at the end of five years. Actually the over all percentage of five year survivals (38 per cent) obtained by Taussig compares unfavorably with the results in patients with Stage II lesions treated with radiations alone in other clinics.

Surgery is the treatment of choice of *sarcomas* but rarely are they diagnosed in the operable stage.

**RADIOTHERAPY**—Soon after the discovery of radium, sporadic assays were made by different workers in the treatment of carcinoma of the cervix as well as other forms of cancer. Cleaves is credited with one of the first attempts (O'Brien). In 1914, Heyman (Sweden) started the first systematic study of the treatment of inoperable carcinomas of the cervix with radium and demonstrated that curietherapy was successful in a small group of these cases. In succeeding years he was rewarded in his effort by the enthusiasm of the Swedish gynecologists who referred to him a considerable number of operable cases. He soon demonstrated that skillful curietherapy was also successful in the operable group. All the early trials of treatment of carcinoma of the cervix by radiations consisted of an internal application of radium. Little, if anything, was expected from external irradiation which was mainly used for palliation of the hopeless cases. As the techniques of radiumtherapy were perfected and rapidly assimilated by surgeons, gynecologists, and radiotherapists, it became evident that the results of curietherapy were not only superior to those of surgery in the treatment of early carcinomas of the cervix, but also that it was a safer procedure giving the patient, even when it failed a longer period of survival. The climax of this controversy came in 1932 with the academic dis-



ceived sufficient treatment to prevent a rapid recurrence. A period of ten days to two weeks may be considered a reasonable interval between treatments.

There are numerous techniques of intracavitary curietherapy for the treatment of carcinoma of the cervix, most of which are minor modifications of the three which we describe summarily below. These techniques all have in common the use of a "tandem," or flexible rubber tube containing aligned radium needles, which is introduced in the uterine cavity. The main differences are concerned with the vaginal application, the amount of radium used, and the duration of the treatment.

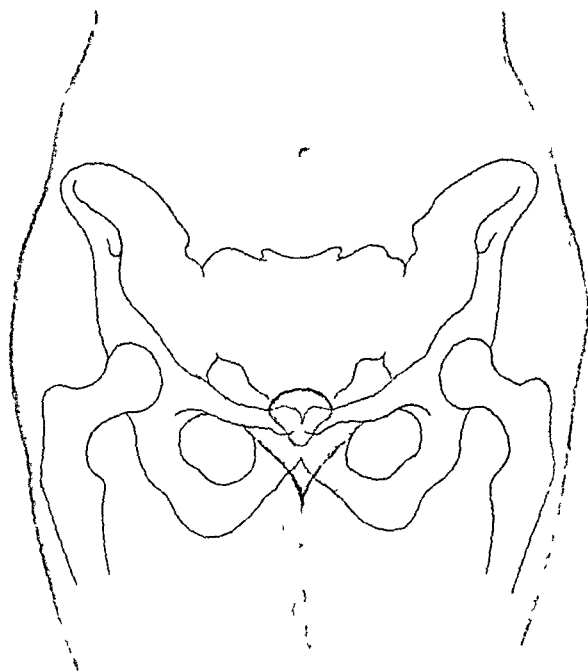


Fig 616—Anterior approach for the external irradiation of carcinoma of the cervix. Notice relatively low position of the uterus.

The *Radiumhemmet* technique consists of the simultaneous insertion of an intrauterine "tandem" and specially fitted vaginal applicators (Fig 622). Three short treatments are given at intervals of two weeks. The total dosage so delivered may be as high as 8,000 to 10,000 mg hr, two-thirds delivered in the vagina and one-third in the uterus.

The *Radium Institute* technique consists of a vaginal application by means of Regaud's colpostat (Fig 621), a total dose of between 3,500 to 4,000 mg hr being given in four to five days. This is immediately followed by the intrauterine application of a "tandem" by which an equal dose of 3,500 to 4,000 mg hr is given in the following four or five days.

per cent) were free of disease at the end of five years. Although these patients received a very thorough external irradiation, there obviously would have been a higher percentage of cures if the treatment had been completed by internal therapy. The series, however, proves that external irradiation is a powerful agent in the treatment of the two last stages of the disease. It also suggests that with the advent of "supervoltage" radiations, the elimination of internal irradiation is a possibility of the future. But as a matter of practice today, external pelvic irradiation should always be followed by internal treatments.

In administering external roentgentherapy, the dimensions of the pelvis and the superficial projection of the uterus and parametria should be taken into consideration. In general the portals of entry do not need to be excessively large (8 by 10 cm). Four portals of entry, *two inguinoliac* (Fig 616) and *two lumbosacral* (Fig 617), are classical fields in use. In some clinics two lateral fields are added, but the use of these fields adds little to the depth dose at the level of the tumor and leads to bone complications which, in our opinion, proscribe its use (Figs 619 and 620). Stamford and Kerr reported twelve cases of fracture of the head of the femur in a series of 1372 patients with carcinoma of the cervix, and concluded that this small incidence (0.87 per cent) did not seem to justify the abandonment of the lateral fields, the majority of the fractures however, occur two to three years following treatment, and the proportion should be estimated on the basis of the survivors rather than on the total number of patients treated. More beneficial than the lateral fields are the *sacroscrotic* portals of entry which have not yet known a great popularity (Fig 618). These are posterolateral fields which bring the radiations into the pelvis through areas in which only soft tissues are present. This contributes greatly to the amount of radiations that ultimately reaches the parametria.

In patients with a small pelvic diameter and who weigh around 100 pounds, the amount of radiations which can be administered through six fields (although compatible with a good condition of the skin) may surpass the limits of compatibility with the normal structures of the pelvis, namely, the bowel. Consequently, a physical evaluation of depth doses on the basis of the pelvic diameters is pertinent in every case in order to establish the total skin doses to be given. In the average case, however, the maximum irradiation given through the six portals (with 200 kv in from six to eight weeks) is seldom sufficient to bring about bowel damage.

The ideal course of external pelvic roentgentherapy allows a protraction over a period of at least six weeks in order for the radiotherapist to manage the general and local reactions without difficulty and in order to diminish the percentage of late accidents due to this form of treatment. The results of external irradiation by means of large amounts of radium element (4 to 10 Gm.) has not contributed better results although its use has furnished remarkable effects in skilled hands (Reverdy).

*Intracavitary Curiotherapy*—It is not advisable to allow a long period of time to elapse between the external treatments and their completion by intracavitary curiotherapy. Although the tumor may have been reduced in size and generally affected by external irradiation, it has not in all probability, re-

surrounding soft tissues of the pelvis. The advantage of this procedure lies in the fact that large doses may be administered to the tumor area. Unfortunately, homogeneity of the irradiation so delivered is lacking and the treatment is sometimes followed by radionecrotic accidents to the surrounding structures. Pitts and Waterman have reported some good results from this type of treatment, but although their over-all statistics are a credit to their unusual skill, the generalization of this therapy increases the possibilities of accidents without improving the results. The procedure is not successful in the moderately advanced cases.

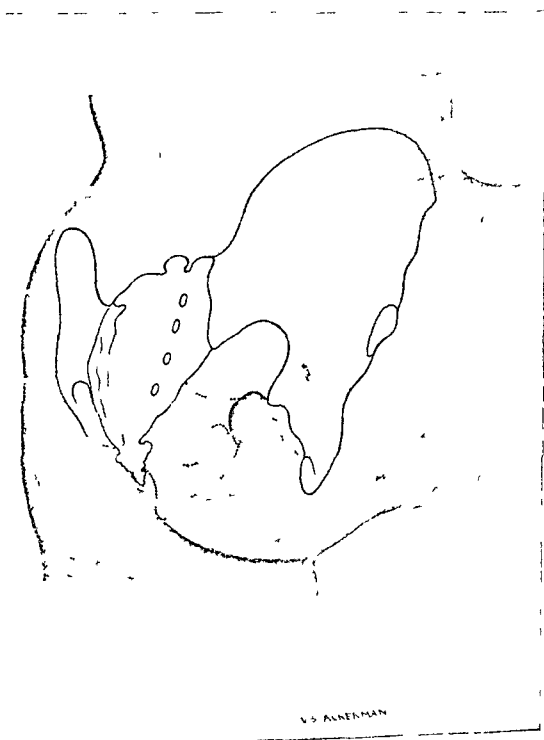


Fig. 618—Posterolateral approach for the external irradiation of carcinoma of the cervix. The sacrospinous notch allows passage of radiations through soft tissues.

*Transvaginal Roentgentherapy*—Despite earlier sporadic attempts, Merritt is to be credited with the first systematic study of transvaginal roentgentherapy as a substitute for intracavitary curietherapy (Fig. 624). The procedure affords several advantages: (1) a more homogeneous irradiation of the affected area, (2) elimination of complications due to secondary infection, (3) its applicability to ambulant patients, and (4) the elimination of radionecrotic fistulas (Regato). Whether transvaginal roentgentherapy will be more successful than the classical curietherapy can be demonstrated only by the statistics of results which are yet

The *Memorial Hospital technique* requires the use of radium emanation which is only available in the large cancer centers. The intrauterine application by means of a "tandem" is straightway succeeded by the intravaginal application of a radium emanation "bomb." This "bomb" is a euphonic receptacle which is directly applied in contact with the cervix and is provided with adequate protection for the bladder and rectum (Fig 623). The dose so administered is slightly larger inside the uterus. The total duration of treatment is about five days.

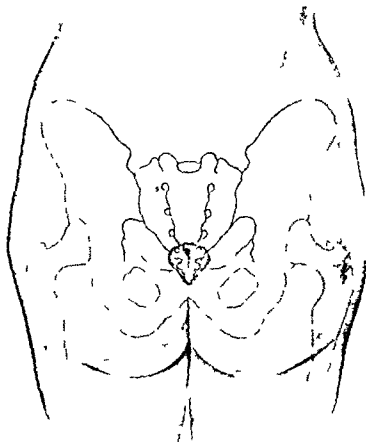


Fig. 61 - Posterior aspect for the intravaginal application of radium in case of the cervix. Notice topographic projection of the uterus.

As can be seen, the different techniques differ mostly in the variety of vaginal applicators. An interesting set of vaginal applicators was developed at the Holt Radium Institute of Manchester. These are rubber ovoids used in pairs with a special spacer. The ovoids are molded so that the outer surface conforms with the isodose curve of the contained radium (Cantril). Whatever the technique used, treatments should be planned individually to adapt it to the requirements of the case. Protraction of the treatment results in diminution of injuries (Cantril).

*Interstitial Curiotherapy*—This treatment consists of introducing needles containing radium element or radium emanation into the tumor itself and the

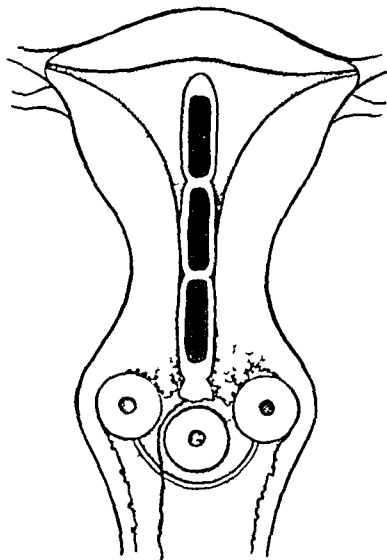


Fig 621

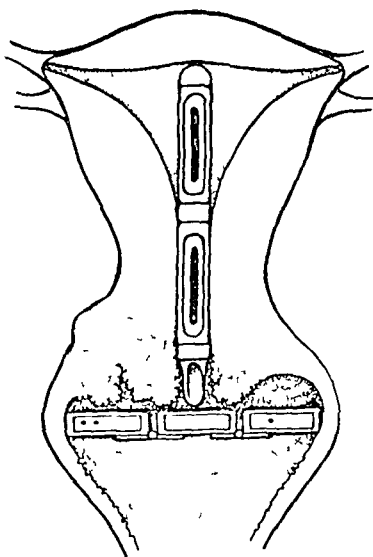


Fig 622

Fig 621 —Radium Institute technique of curietherapy. Intrauterine tandem and vaginal colpostat with an additional cork applicator in the center. The intrauterine and vaginal treatments are not simultaneous. The entire treatment is protracted over eight to ten days.

Fig 622 —Radiumhemmet technique of curietherapy. Simultaneous intrauterine and vaginal treatment by means of a metal tandem and varied vaginal applicators. Three massive doses are given in twenty-four hours at intervals of two to three weeks.

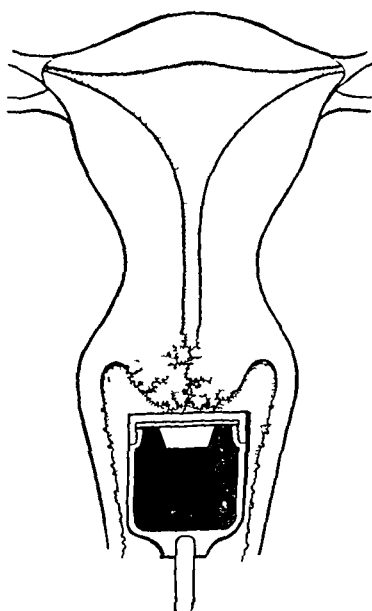


Fig 623 —Memorial Hospital technique of curietherapy. The intrauterine application by means of a tandem is followed by intravaginal application of a radium bomb (a receptacle containing a large amount of radium emanation which allows protection of the rectum and bladder).

to be contributed. We believe that because this method offers definite advantages, it will become the method of choice in the future. In our hospital fifty-two consecutive patients with carcinoma of the cervix in all stages received external irradiation followed by transvaginal roentgentherapy. After a three-year control period there were twenty-three patients (42 per cent) living and well (Regato).



Fig 619—Avascular necrosis of the head of the right femur after irradiation through large lateral pelvic fields for carcinoma of the cervix.

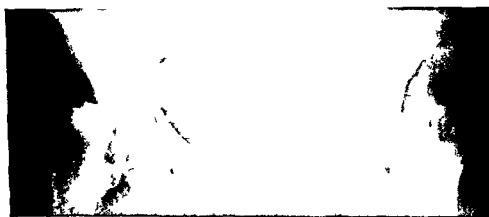


Fig 620—Bilateral fractures of the heads of the femurs following irradiation through lateral pelvic fields for carcinoma of the cervix. The patient remained cured of carcinoma.

*Early Complications of Radiotherapy*—The most common complications found in the course of radiotherapy of carcinoma of the cervix are those due to secondary infection. For a long time these infections have caused the interruption or discontinuation of treatments which have then ended in failure. In general external irradiation succeeds in diminishing the secondary infection and in improving the general condition enough to counteract further complications. But when radium is used as a complementary step trauma and vaginal picking may bring about exacerbations of infection. Garofa reported that although external pelvic irradiation was done first 71 per cent of his patients had repeated elevations of temperature above  $101^{\circ}\text{F}$  during the course of treatment.

*constitute an unavoidable consequence of radiotherapy treatment* If the treatment is adequately conducted (with proper balance of size of field and daily dose and progressive increase of daily dose), the overwhelming majority of patients will conclude treatment without nausea. During the course of treatment a more or less marked *diarrhea* usually develops, but this functional reaction of the bowel should not cause alarm unless it becomes excessively prominent. It usually requires administration of an antidiarrheic. Bismuth should not be used during treatments because of the secondary radiations which such products might add to the bowel mucosa. If the diarrhea becomes acute and bloody, a revision of the daily and of the intended total dose may be indicated, and treatment may even have to be interrupted.

The total amount of radiations administered may cause a dry or exudative *radioepidermitis* of the skin. This skin reaction, already described in the chapter on radiotherapy, is harmless and reparable on the condition that it be kept free from secondary infection. This implies daily dressings during the period in which the epidermis is absent in the exudative type. The necessity for these daily dressings under competent surveillance cannot be sufficiently emphasized, for these precautions will prevent the development of telangiectasia, fibrosis, atrophy, and late radionecrosis of the irradiated areas, but, if neglected, the secondary infections penetrate the dermis and a *radiodermatitis* may immediately result. Damage to the dermis is not easily healed and may possibly require surgical excision and skin grafts.

Following the application of radium, an area of *radioepithelitis* of the vaginal mucosa always develops, appearing in the form of a diphtheroid membrane more or less limited to the upper third of the vagina. This mucosal reaction spontaneously subsides under proper antiseptic care but, if neglected, may develop into radionecrosis as in the case of the skin. Fortunately, the vagina has a great ability to repair itself, and many of these localized radionecrotic accidents are passed unnoticed. Proper vaginal douches and antiseptic jellies are adequate preventive measures.

Following the application of radium there may be a mild degree of *proctitis* caused by the reaction of the rectal mucosa. If the radium comes in contact with the rectum and the dose is large, a localized radionecrotic area may develop on the anterior rectal wall at the level of the cervix. A certain amount of rectal bleeding may appear accompanied by pain and tenesmus. These small areas of necrosis often heal spontaneously. *Cystitis* is rarely observed.

A *rectovaginal* or a *vesicovaginal* fistula may appear in the course of treatments or immediately afterward, but these accidents are not necessarily due to excessive irradiation. If tumor has invaded the rectovaginal septum or the bladder, the destruction of the tumor opens a passage which results in a urinary or fecal fistula. This is particularly evident in advanced cases after a massive dose of radiations has been given. The production of vesicovaginal or rectovaginal fistulas due to irradiation can be avoided by properly packing the radium applicators in the vagina.

*Late Complications of Radiotherapy*—External and intracavitary irradiations may result in an overirradiation of the vital organs of the pelvis. A small

Two thirds of these cases ended with an incomplete treatment and consequently the total survival rate was considerably diminished. The most common infectious complications were pelvic cellulitis, pelvic peritonitis, urinary infection, and pyometra, a great proportion of which occurred in the young patients. The virulence of the secondary infection is an important factor, but the resistance of the patient is perhaps even more relevant. Investigation of this balance of

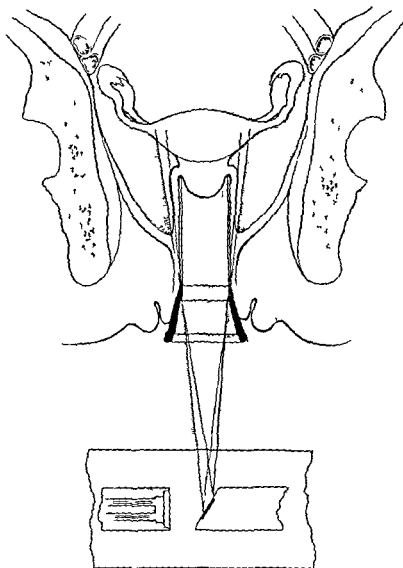


Fig. 64—Transvaginal roentgen therapy. Irradiation through a specially designed speculum (Regato) which protects the vulva while allowing dispersion of the beam through its walls.

factors may be made by means of the Ruge-Phillipp test in which the vaginal secretion is cultured in the patient's own serum. With the advent of the sulfonamides and penicillin, these complications have now been considerably reduced and the Ruge-Phillipp test is no longer justified.

The use of moderate sized portals and appropriate daily doses eliminates the general reaction known as "irradiation sickness." This general reaction does not



## Prognosis

Carcinoma of the cervix treated adequately has the best prognosis of all major forms of cancer. Although an early diagnosis is desirable and offers a greater chance of cure, the curability of even advanced carcinomas of the cervix is remarkable.

It is perfectly safe to judge the results of treatment on a five-year-cure basis. Regaud made a study of 559 cases of carcinoma of the cervix in which radiotherapy had failed and found that 86 per cent died within three years, and although twenty-eight patients died after five years, only two of these did not show evidence of recurrence within the five-year period (Fig 625).

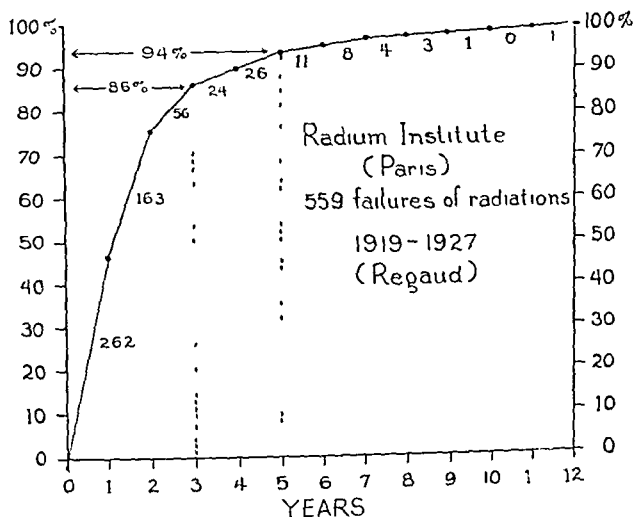


Fig 625—The overwhelming majority of patients who die following a failure of radiotherapy do so within five years. In this large series only twenty-eight patients died after five years and of these only two did not show their recurrence before five years.

Of 5,669 cases treated between 1914 and 1931 by nine different institutions and collected by the League of Nations, 1,489 patients (26 per cent) remained well after five years (Table LII). These statistics represent an over-all average of results over many years and also an average which includes different qualities of treatment. In certain institutions the figures have been consistently

TABLE LII COMPILED RESULTS OF RADIOTHERAPY IN CARCINOMA OF CERVIX TREATED IN NINE DIFFERENT INSTITUTIONS FROM 1914 TO 1931

(Data from Heyman, J. Acta obst & gynec. Scandinav., 1938)

	CASES*	WELL 5 YEARS†	PERCENTAGE
Stage I	607	335	55
Stage II	1,625	590	36
Stage III	2,417	512	21
Stage IV	1,020	52	5
Total	5,669	1,489	26

\*Cases incompletely treated are included

†Patients dead of intercurrent diseases before five years were considered as failures

amount of rectal bleeding and sometimes a rectal hemorrhage, usually accompanied by "gas pains," may occur in patients who have been well for some time. The bleeding may be due to the untoward effect of radiations on the large or small intestine or on both, but these symptoms are neither frequent nor necessarily fatal. Prompt administration of sulfasuxidine, penicillin, and, if necessary, blood transfusions may be sufficient to facilitate total and permanent recovery. In a few instances there is bowel obstruction and then an enteroenterostomy or a colostomy may become necessary. When lateral fields of irradiation have been used or oversized fields of entry have been applied to a small pelvis, *vascular changes of the pelvic bones* and later spontaneous fractures may result particularly at the head of the femur (Figs 619 and 620). Avoidance of this portal of entry eliminates this complication.

An area of heavily irradiated skin may be the site of a *late radiodermatitis* occurring several years after treatment. As a general rule there is a history of trauma (or surgical incision) and subsequent secondary infection which brought into a devitalized area of the skin contribute as much to this accident as the radiations themselves. To avoid such late radionecrosis the patient should be cautioned against allowing excessive dryness of the irradiated area of the skin.

Late *rectovaginal* or *vesicovaginal fistulas* may result years after the carcinoma has been controlled purely from the effects of irradiation of these structures. More frequently, however, these late complications accompany a recurrence, which causes secondary infection and consequent necrosis.

*Causes of Failure of Radiotherapy*—The most common cause of failure of radiotherapy is an insufficient irradiation of all potential tumor areas. Obviously, complications which interrupt the course of treatment easily lead to underdosage but, in addition, it is possible that secondary infection diminishes the radiosensitivity of these tumors. Faulty technique and the displacement of radium applicators may result in underdosage and consequently in local recurrences (Wirth). But in addition, when the parametria have been invaded, an insufficient external irradiation is most frequently the cause of failure in spite of a perfect internal irradiation. Compression or invasion of the ureters resulting in uremia usually impedes completion of treatment. In some cases however, full return of ureteral function is reestablished by radiotherapy (Cantril).

Upper abdominal metastases outside of the field of irradiation may be present during the course of treatments and may result in generalization of the disease even when the tumor has been totally sterilized in the pelvis. With the improvement of radiotherapeutic techniques, this phenomenon is being observed more often. Finally, the untoward effect of radiations on the small or large bowel may result in a large area of necrosis which can cause death but this is exceptional (Aldridge). In general, most bowel complications properly handled medically or surgically are not fatal.

In a thorough study of a small group of early carcinoma of the cervix Buschke traced most failures to a definite avoidable inadequacy of the treatment. Lack of radiosensitivity of the tumor, although sometimes claimed as a cause of failure is seldom if ever, the cause of recurrences.

real handicaps. On the other hand, Jones, reporting the results obtained at the Kelly Clinic, related that patients with Stage I carcinoma had been divided into two groups—those with the very early lesions being operated on and the others treated by radiotherapy. At the end of five years the good results showed a considerable partiality for the group treated by radiotherapy. In other institutions the results of radiotherapy in the treatment of Stage I carcinoma have shown as much as an 80 per cent five-year survival rate (Table LIII).

TABLE LIII RESULTS OF RADIOTHERAPY IN TREATMENT OF STAGE I CARCINOMA OF CERVIX

	YEARS	CASES	WELL 5 YEARS	PERCENTAGE
League of Nations (Heyman)	1914 1931	607	335	55
Radium Institute (Regaud, Paris)*	1925 1929	37	28	76
Marie Curie Hospital (Hurdon, London)*	1934 1937	40	32	80

\*Results of intracavitary curietherapy alone without benefit of adjunctive external pelvic roentgentherapy.

*Stage II*—The results in this group of already moderately advanced cases are rather satisfactory under the judicious combination of external and internal radiotherapy. The prognosis has been reported as varying from 35 to 60 per cent five-year survivals (Table LIV).

TABLE LIV RESULTS OF COMBINED EXTERNAL AND INTRACAVITARY RADIOTHERAPY IN TREATMENT OF STAGE II CARCINOMA OF CERVIX

	YEARS	CASES	WELL 5 YEARS	PERCENTAGE
League of Nations (Heyman)	1914 1931	1,625	590	36
Johns Hopkins (Jones, Baltimore)	1927-1935	124	50	40
Radiumhemmet (Heyman, Stockholm)	1931 1938	849	362	42
Radium Institute (Regaud, Paris)	1926 1931	217	100	46
Marie Curie Hospital (Hurdon, London)	1934 1937	174	107	61

*Stage III*—It cannot be sufficiently emphasized that a *Stage III carcinoma of the cervix has a better prognosis than an operable carcinoma of the stomach* (Regato). This fact ought to encourage and promote the attention given to this group of cases. What is usually called a "frozen pelvis" is often a curable *Stage III carcinoma of the cervix* and should never be considered as hopeless. The results obtained in this group, however, are invariably due to a thorough external irradiation. The five-year rates for these patients vary from 20 to 34 per cent (Table LV).

TABLE LV RESULTS OF COMBINED EXTERNAL AND INTRACAVITARY RADIOTHERAPY IN TREATMENT OF STAGE III CARCINOMA OF CERVIX (THE RESULTS IN THIS GROUP MAY BE TAKEN AS A MEASURE OF QUALITY OF EXTERNAL IRRADIATION GIVEN IN DIFFERENT INSTITUTIONS)

	YEARS	CASES	WELL 5 YEARS	PERCENTAGE
League of Nations (Heyman)	1914 1931	2,417	512	21
Radiumhemmet (Heyman, Stockholm)	1931 1938	561	117	20
Memorial Hospital (Healy, New York)	1928 1931	308	68	22
Marie Curie Hospital (Hurdon, London)	1934 1937	455	143	31
Radium Institute (Regaud, Paris)	1926 1930	226	77	34

improving Heyman reported that of 1885 patients treated at the Radium hemmet between 1914 and 1930, 412 (22 per cent) were free of disease after five years, while of 1,920 patients treated between 1931 and 1938, 606 (31 per cent) remained well after five years. This improvement is still further enhanced by considering the results in the last year reported (1938), when of a total of 336 patients treated, 131 (40 per cent) were well and free of disease five years after. The judicious application of "superfoltage" radiations has brought about a definite improvement of results. Buschke and Cantrell reported the results of external pelvic irradiation with 800 kv plus intracavitary curie therapy. On a selected group of 130 patients thus treated at the Tumor Institute of the Swedish Hospital, in Seattle fifty six (43 per cent) survived five years.

It has been suggested that carcinoma of the cervix has a less favorable prognosis in younger women, but Laborde found no appreciable difference in the outcome of the different age groups in fifty seven patients with Stage I carcinoma of the cervix. The histologic grading of epidermoid carcinomas of the cervix does not provide a basis for prognosis. However in a group of patients in the same clinical stage, those few presenting very undifferentiated carcinomas (Grade III) may be considered as having a less favorable prognosis.

Adenocarcinomas have been regarded for a long time as having a less favorable prognosis than the more common epidermoid carcinomas. However, Baclesse (1942) in this regard reported on a series of forty patients with adenocarcinomas treated at the Radium Institute of Paris of whom twelve (30 per cent) remained well after five years. He then compiled 420 cases of adenocarcinomas of the cervix from the world literature and found that 101 (24 per cent) of the patients were reported well five years after radiotherapy.

The most important single factor influencing the prognosis is secondary infection, mainly because it can and usually does interfere with the completion of treatment. Garcia reported that the results were less satisfactory in Negro women but this may have been due to the fact that more of these cases presented secondary infection. Recurrences following any kind of treatment usually have a very poor prognosis. Carcinomas of the cervix which recur after radiotherapy (adequate or inadequate) have a very meager chance of being cured by a second treatment. Recurrences after total hysterectomies also yield very poor results because in the majority of instances the tumor is already disseminated within the pelvis.

It is important to analyze the results in the different stages because this usually emphasizes the necessity of improvement of one or the other aspect of the treatment.

*Stage I*—Cases of carcinoma of the cervix in this initial stage are highly curable both by surgery and radiotherapy provided the treatment is applied with proficiency. Emmert reported on a series of forty one patients with Stage I carcinoma of the cervix operated on at the Barnard Skin and Cancer Hospital of whom thirty three (80 per cent) were cured. In the same institution only those patients who were inoperable because of obesity, hypertension, diabetes or cardiorenal disease were treated with raditions. Of twenty seven patients in this category, 60 per cent were cured, a very good result considering the clin

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**Stage IV**—Under the revised classification of 1937, the cases which fall in Stage IV are most advanced. A very restricted number of these carcinomas have been permanently sterilized, however, even after tumor had perforated into the bladder or rectum (Table LVI). The results of external and internal treatment for the majority of these Stage IV cases yield only a worthwhile palliation.

TABLE LVI RESULTS OF COMBINED EXTERNAL AND INTRACAVITARY RADIOTHERAPY IN TREATMENT OF STAGE IV CARCINOMA OF CERVIX (CLASSIFICATION OF 1929 BEFORE ITS REVISION IN 1937)

	YEARS	CASES	WELL 5 YEARS	PERCENTAGE
League of Nations (Heyman)	1914-1931	1,020	52	5
Memorial Hospital (Healy, New York)	1928-1931	79	5	6
Marie Curie Hospital (Hurdon, London)	1934-1937	138	10	7
Radiumhemmet (Heyman, Stockholm)	1931-1938	248	21	9

In summary, it is clear that pessimism is not justified in the treatment of carcinoma of the cervix and that the time and expense involved in administering an adequate treatment to most of these cases will be amply rewarded by the satisfying results.

The prognosis of *sarcomas* of the cervix is admittedly very poor.

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## CARCINOMA OF THE CERVICAL STUMP

The cervical stump is the portion of the cervix which is left after a supra vaginal hysterectomy has been performed. The uterus is usually amputated at the isthmus, 1.5 to 2 cm above the free extremity of the cervix. The cervical canal is obliterated to a maximum depth of 1.5 to 2 cm but the lymphatic drainage of the remaining cervix is practically untouched (Fig 626).

Carcinoma may develop in the cervical stump twenty five years or more after a subtotal hysterectomy. The actual incidence however is not known for actual figures are difficult or impossible to obtain inasmuch as there is less strict follow up of general surgical cases as compared with cancer cases. Many of the cases reported in the literature as carcinoma of the cervical stump developed shortly after hysterectomy and were in all probability carcinomas of the cervix or endo cervix which were not suspected at the time of operation (Martzloff). More often quoted in the literature is the proportion of carcinomas of the cervical stump seen in the specialized clinics and expressed in percentages of the total number of carcinomas of the cervix. These percentages run as high as 4 or 5 per cent but are misleading and should not be taken as representing incidence.

In view of the fact that carcinomas may develop in the remaining cervix several outstanding surgeons hold the belief that this justifies doing a pan



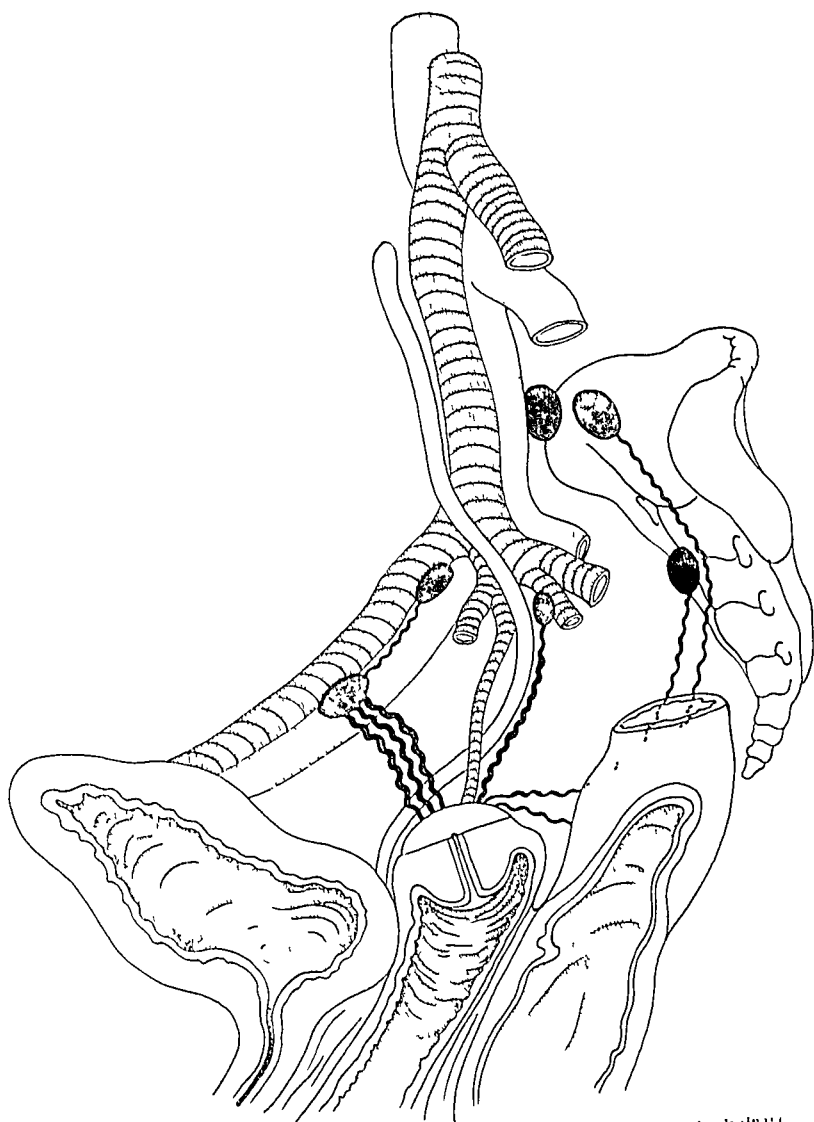


Fig. 626.—Schematic representation of a cervical stump and its lymphatic drainage.



## Prognosis

At present, the prognosis of carcinoma of the cervical stump is slightly less favorable than that of carcinoma of the cervix. However the published results today are rather encouraging. Fricke and Bowing reported on fifty-seven patients with carcinoma of the cervical stump treated at the Mayo Clinic of whom fifteen (26 per cent) were free of disease five or more years after the treatment. Monod reported ten of twenty-seven patients free of disease from two to ten years. Healy and Arneson treated sixty-seven patients at the Memorial Hospital of New York, with 14 per cent five-year cures. Cantlil and Buschke have reported five of eight patients well and free of disease five years after treatment.

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## CARCINOMA OF THE CERVIX AND PREGNANCY

Carcinoma of the cervix is an infrequent complication of pregnancy because carcinomas of the cervix are more frequently found in women between 45 and 55 years of age when reproductivity is over and because pregnancy seldom occurs in a woman who already has carcinoma of the cervix. The incidence of this association has been variously estimated as 1 in 1,000 to 1 in 20,000 pregnancies. It is found predominantly in women between 30 and 40 years of age (Strauss).

During pregnancy the cervix is subjected to an increased blood circulation with hypertrophy of the muscle and connective tissue. Moreover the columnar epithelium of the endocervix is replaced by cuboidal cells and there is marked subepithelial proliferation extending deeply into the connective tissue. These histologic changes, no matter how impressive do not necessarily lead to carcinoma, but carcinoma which develops on the cervix of a pregnant uterus is reputed to be able to develop much faster than in the absence of pregnancy. A few authors believe that carcinoma develops faster due to hormonal stimulants and have reported an arrest in the development of the tumor with the end of gestation but this is not corroborated by the majority (Richman). The rapid development of carcinoma during pregnancy could be explained on the basis of increased blood supply and of added young connective tissue on which the tumor develops. This however, is purely theoretical.

When carcinoma of the cervix develops in the early stages of pregnancy or when pregnancy has occurred in spite of the presence of carcinoma of the cervix, the chances of an early spontaneous abortion due to infection are great.

hysterectomy, their main contention being that the operative mortality of total hysterectomies is not any higher in skilled hands. Several factors, however, have to be considered before advocating this radical course. Many of these operations are done for inflammatory diseases and the risk involved is obviously greater for the larger operation, the operative mortality is unquestionably higher in the hands of the average surgeon, morbidity becomes an important factor, for it is generally accepted that a panhysterectomy carries greater possibilities of injury to the bladder and the ureter and, finally, it should not be forgotten that carcinomas of the cervical stump are curable in an appreciable proportion. The problem is usually presented as a question of balance between the greater operative mortality of the radical operation and the incidence of carcinoma in the remaining cervix. We think that the question should be presented as a balance between the increased operative mortality in the hands of the average surgeon and the number of carcinomas of the cervical stump which once developed may fail to be cured.

Much too often are subtotal hysterectomies performed in cases of vaginal bleeding without a previous dilatation and curettage for diagnostic purposes. In these cases, a carcinoma of the endocervix may be severed and the subsequent pathologic examination reveal the error. In other cases the entire tumor may be left behind and the diagnosis not established for some time. Some of these cases, particularly the adenocarcinomas of the endocervix, may continue to develop so slowly that further treatment is not sought for two to three years. These cases do not constitute true carcinomas of the cervical stump. Carcinoma may, of course, develop on the remaining cervix at any time after the operation, but it is better for statistical purposes not to consider as carcinomas of the cervical stump those cases in which the symptoms have appeared within three years. A uterine myoma present at the time of operation does not eliminate the possibility of a coexisting but overlooked carcinoma of the cervix.

Some authors report that it is a rule the diagnosis of carcinoma of the cervical stump is made later than the diagnosis of carcinoma of the cervix in general. Cantrell and Buschke, however, found a large proportion of early cases and attribute this finding to the fact that patients presenting vaginal bleeding after a subtotal hysterectomy are more often alarmed than those with no previous operation.

### Treatment

It is in the practicability and the results of treatment that carcinoma of the cervical stump differs most from carcinoma of the cervix. An important step in the treatment of carcinomas of the cervix is the intracavitary irradiation by introduction of a "iridium" in the cervical canal. This procedure is practically impossible in carcinomas of the cervical stump because of the shortness of the canal. The result is a diminution of the total dosage and a consequent greater possibility of local recurrence.

Transvaginal roentgentherapy as a complement of external irradiation is probably the best treatment for carcinomas of the cervical stump. Its use may become more widespread after its superiority is proved by statistics of results.

integral part of the host and that it has local invasive qualities normally. Normal trophoblasts may show abnormal cytologic changes, but even when they show all degrees of anaplasia, if they are not in contact with the uterine wall, invasion cannot take place. This undoubtedly explains the failure of correlation at times of microscopic appearance of hydatidiform moles and subsequent clinical course. Hertig has emphasized that at least ten representative sections of the mole should be taken, and, most important, that *the curettings taken at the time of molar evacuation should be meticulously studied*. He considers four histologic types of "malignancy": chorionepithelioma in situ, syncytial endometritis, chorionadenoma destruens, and chorioncarcinoma. He has detailed the histologic criteria of these types and emphasized that the first three of these are of only questionable "clinical malignancy," although microscopically they show changes which Hertig believes significant. It is in the last group only, that a rapid malignant course can be expected. Of 200 cases of hydatidiform mole, Hertig found that seven were chorionepitheliomas in situ, nine were syncytial endometritis, thirty-two were chorionadenoma destruens, and only five were chorioncarcinomas. The 5 patients with chorioncarcinoma died. Only two other patients died, and both of these were postoperative deaths. It is, therefore, logical that a conservative attitude of "scientific, apprehensive expectancy" should be adopted when dealing with a hydatid mole. In this fashion, many needless operations may be avoided without added risk.

### Treatment

Treatment of carcinoma of the cervix during gestation may imply dramatic decisions. Two important factors are involved: the life of the child and the risk incurred by the usually young mother. In addition, the stage of advancement of the tumor and the stage of development of the pregnancy must both be considered.

**First Half of Gestation**—It is generally accepted that during the first four or five months of pregnancy the fetus should be sacrificed in the interest of the mother. When this decision is reached, treatment should be started by external pelvic roentgentherapy just as for carcinoma of the cervix in the non-pregnant uterus. After a period of four to six weeks, a therapeutic abortion occurs in the majority of cases. When this does not take place, a dilatation of the cervix and a curettage of the uterine contents should be performed, for the fetus ought not reach term after this irradiation. Irradiation of the fetus during the early months of pregnancy results often in anatomic and mental deficiencies of the child (Murphy). After the abortion, treatment should be continued in the usual manner. In the early lesions which are commonly associated with early pregnancies, a total hysterectomy may be equally successful. It has the advantage of being expeditive.

If the patient objects to a therapeutic abortion, external roentgentherapy should not be given. Intravaginal curietherapy during the earlier stages of pregnancy also implies damage to the fetus and most often also results in abortion (Fig. 627). The application of small amounts of radium may not produce an abortion but does not have sufficient effect on the tumor to sterilize it.

Vaginal bleeding may persist and become alarming, but in the majority of instances it is rather mild. Lumbar pain spreading to the hip and thigh may be present after the tumor has invaded the parametrium.

When the tumor is not discovered and delivery "per vias naturales" is allowed to occur, deep lacerations and fatal hemorrhage may follow, although in some early lesions, delivery has been relieved. In other cases however, the patient may die undelivered because of obstruction by the tumor.

Repeated or prolonged bleeding during gestation often leads to an early diagnosis of carcinoma of the cervix. In general, in order for impregnation to occur in the presence of a carcinoma of the cervix the tumor must not be very advanced and if the impregnation has preceded the tumor, then it has not been present for long when it is discovered. The symptomatology is usually and unfortunately attributed to other more common complications of pregnancy. As a rule bleeding is taken for a symptom of abortion and the conservative management of threatened abortion is usually given. If inspection and palpation of the cervix reveal an area of ulceration and induration the greatest care should be exercised to obtain a biopsy. In the early stages of pregnancy a lacerated, everted cervix with an irregular easily bleeding center may be taken for a carcinoma. The decidual reaction of the endocervical epithelium could also be mistaken microscopically for early carcinomatous changes. Nonspecific proliferative lesions of the cervix can also be mistaken for carcinoma but the biopsy will easily solve the problem of diagnosis. When the patient is first seen toward the end of pregnancy a large soft exophytic carcinoma may be mistaken for a spongy placenta previa an error possibly fatal to the patient.

In the differential diagnosis of carcinomas of the cervix during pregnancy one should consider the *hydatidiform mole* which is equally rare. This tumor occurs as a complication of pregnancy and is composed of cysts that are a product of cystic degeneration of the stroma of the villae. There is usually severe bleeding during the early months of pregnancy. Fortunately the diagnosis is rather simple in view of the characteristic appearance of the cysts which are spontaneously eliminated. The difficulty in the treatment of hydatidiform moles is due to the fact that they may be the basis for the development of *chorioepithelioma*. About half of all chorioepitheliomas develop from hydatidiform moles one fourth after full term pregnancies and one fourth after abortions (Novak). They have a marked tendency to invade the wall of the uterus and the blood vessels and to metastasize distantly. They may be accompanied by fairly large bilateral luteal cysts of the ovaries. Both the hydatidiform mole and the chorioepithelioma may produce large amounts of gonadotropic hormones which should be investigated in the blood and urine but the test does not serve to differentiate between the two conditions. The most difficult decision to make is that of the treatment of the hydatidiform mole which is suspected of degeneration into chorioepithelioma.

Hertig has demonstrated that there is a general correlation between the morphologic appearance of a hydatid mole or of its curettings, with the subsequent development of chorionic "malignancy." It should be noted that the normal trophoblast is different from the ordinary tumor cell in that it is not an

soon as the child is viable) and then proceed with the regular course of treatment. Hysterectomies are accompanied by a greater operative mortality when done on these patients.

**Term of Gestation**—Many cases of carcinoma of the cervix are diagnosed at the time pregnancy has reached its full development. If the carcinoma is a very early one, delivery may be chanced "per vias naturales" with the use of forceps as a protective measure against possible lacerations. If, however, the lesion does not warrant this risk, a cesarean operation should be done and the carcinoma treated later by the regular radiotherapeutic methods.

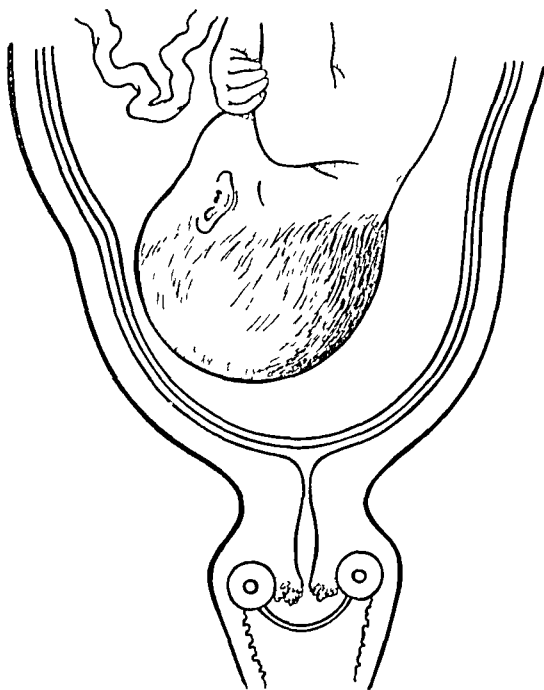


FIG. 628.—Intravaginal application of radium in late pregnancy. Only the presenting part of the fetus is irradiated and permanent damage is not necessarily implied by therapy.

**During Labor**—Carcinoma of the cervix which is discovered during the first stage of labor affords little opportunity for deliberation. If the tumor does not appear to allow complete dilatation of the cervix and a cesarean section is still possible, it should be performed immediately. A Porro section is preferable (Danforth). If the cervix is already considerably dilated, the use of forceps is indicated to avoid lacerations as much as possible, but the consequences are usually grave. If the patient survives delivery, external roentgentherapy should be administered at the earliest possible time and later complemented by internal treatments.

The only alternative left under these circumstances is absolute abstention of therapy in order to allow development of the fetus and delivery by cesarean section. This procedure, which is directed to protect the life of the child at the risk of the mother, often results in the loss of both.

**Second Half of Gestation**—During the last half of pregnancy, it is generally accepted that an effort can be made to preserve the life of the child without endangering the life of the mother or without reducing considerably her chances of being cured.

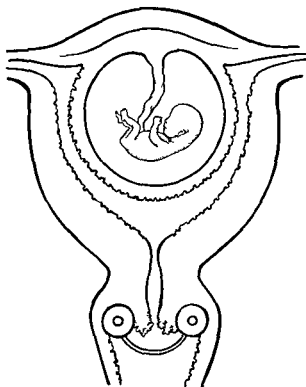


Fig. 627.—Intravaginal curietherapy for carcinoma of the cervix in early pregnancy. The small fetus is inevitably close to the cervix so that most of it is heavily and dangerously irradiated.

The procedure generally consists of a preliminary intravaginal application of radium. At this stage, the possible damage to the child is considerably less than in the early stages because the relative distance of the fetus from the cervix is much greater (Fig. 628). If the diagnosis of carcinoma is made during the fifth or sixth month of gestation, it may be best to wait a month or six weeks before the radium is applied. Following the application of radium, a cesarean section should be done as soon as the child is viable. After cesarean section, treatment should be continued by intrauterine curietherapy. Another procedure to be applied to early lesions consists in applying radium while awaiting the viability of the child and then performing a cesarean followed by hysterectomy (Porro section). Berkeley reported a case so treated: the child was born with bald patches on her head which later were covered by hair, and she grew to be an outstanding athlete. If the tumor is advanced, the intravaginal application of radium without previous external pelvic roentgentherapy is of little value and consequently it may be preferable to do a cesarean operation first (as



urethra and anterior to the rectum. The internal surface of the vagina presents numerous transversal folds. Its upper extremity reflects upon itself to become continuous with the uterine cervix, forming a circular cuff which is arbitrarily divided into four arcs—the anterior, posterior, and lateral fornices. It is in contact with the peritoneum only at the level of the posterior fornix, where it is in relation with the cul-de-sac of Douglas. The lower or outer extremity of the vagina is its narrowest part and is surrounded by the constrictor muscles.

The vaginal wall is 3 or 4 mm thick and is formed by three layers of tissue: an outer, fibrous layer, a middle muscular layer, and an inner mucosa. The mucosa is a stratified squamous epithelium on an irregularly wavy basement membrane. Normally the mucosa has no horny layer and no glands, but these may occasionally be found in the fornices.

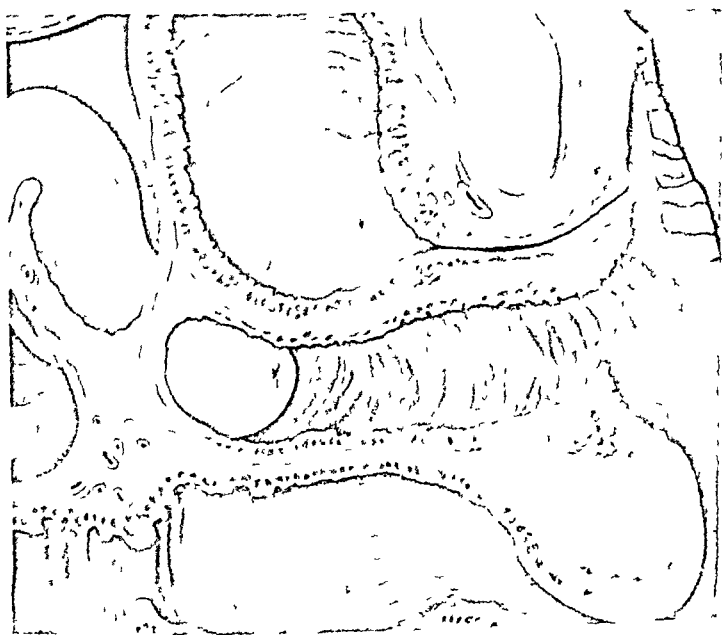


Fig. 629.—Sagittal section of the vagina illustrating its relation to the bladder and rectum.

**Lymphatics**—The lymphatics of the vaginal wall may be divided into two main groups: one accompanying the uterine artery and the other following the course of the vaginal artery (Rouvière). The lymphatics which follow the *uterine artery* drain the superior part of the vagina and empty into one of the nodes of the external iliac chain. The lymphatics which follow the *vaginal artery* drain, for the most part, the lower half of the vagina and empty into one of the hypogastric lymph nodes. In addition, the lymphatics of the vagina anastomose with those of the cervix and of the vulva. Rarely some of them may also penetrate into the rectal wall and terminate in perirectal lymph nodes.

**During Puerperium**—Carcinoma of the cervix which is diagnosed following delivery requires no special technique of treatment and should be managed as all other carcinomas of the cervix.

### Prognosis

Sarvey in 1908 reported a mortality of 53 per cent in patients with carcinoma of the cervix who were allowed to develop to term and were delivered "per vias naturales". Eight per cent of these patients died undelivered. Today the prognosis for the mother is much better than it used to be because the mortality rate has been reduced and the radiotherapeutic results improved.

In the early stages of pregnancy the fetus is lost but the prognosis for the child improves as it reaches viability and the ideal indication of a cesarean section. If the tumor is advanced when the cesarean section is done, the infant mortality is however, high. Conversely the prognosis for the mother is best in the early stages of pregnancy and decreases toward term. Obviously the prognosis of these patients also depends on the stage of development of the tumor which, in the majority of cases, falls within the definition of a Stage I or II.

Large statistics of five year results are not available as the reports of these cases are usually concerned with the technique of management rather than with the long term results. Of twenty patients treated at the Mayo Clinic by different methods and followed more than five years six (30 per cent) remained living and well (Muno).

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## CANCER OF THE VAGINA

### Anatomy

The vagina a muscular membranous very elastic tube extends from the vulva to the uterus and lies immediately posterior to the bladder and the

There is immediate local pain followed later by dysuria and constipation due to constriction of the bladder and rectum. Hematuria and edema of the lower extremities may be observed. Distant metastases are rare in sarcoma of the child but are not uncommon in sarcoma of the adult. Deterioration of the general condition with anemia and uremia rapidly develops.

### Diagnosis

It should be kept in mind that a primary carcinoma of the vagina is less frequent than direct involvement or metastases from primary lesions in other organs. Because of the frequent involvement of the vaginal wall by carcinomas of the cervix, a diagnosis of primary carcinoma of the vagina should not be made unless the cervix is found intact. When an exploration of the cervix is not possible through the vagina, a diagnosis of carcinoma of the vagina should only be done when on rectal palpation the region of the cervix appears normal and the parametria are not involved (Radiological Subcommittee, Committee on Hygiene of the League of Nations). These strict rules are justified because of the rarity of carcinoma of the vagina. Carcinomas of the endometrium may also directly involve or metastasize to the vagina. Because some of these metastatic tumors are undifferentiated and do not show distinct adenoïd arrangements, an erroneous diagnosis of primary carcinoma of the vagina is often made, particularly when the cervix is not affected. Vaginal metastases are very common in uterine chorioepitheliomas, but the differential diagnosis can be based on a recent pregnancy or on the recent elimination of typical hydatid cysts. Malignant tumors of the ovary and carcinomas of the gastrointestinal tract may produce abdominal implants which gravitate to the cul-de-sac of Douglas, where the tumor easily invades the posterior wall of the vagina and simulates a primary tumor of the wall. A dilatation of the cervix and curettage of the endometrium should always be done when the carcinoma is not frankly epidermoid. Very rarely an unsuspected carcinoma of the bladder invades the vagina, and in such advanced lesions there may be a difficulty in establishing the true point of origin.

Sarcomas of the child are easily recognized. The sarcoma of the adult may present itself as a submucous nonulcerated mass of the vaginal wall or as an already ulcerated, necrotic tumor. The diagnosis is made on biopsy.

Most of the benign lesions of the vaginal wall are pedunculated and non-ulcerated and consequently easily diagnosed. Condyloma acuminata usually spread into the vagina from the vulva. Benign ulcerations are superficial and often tender. Tuberculosis and syphilitic ulcerations are rare. Teratomas (dermoid cysts) occur usually in the rectovaginal septum and may be confused in the adult with sarcomas, however, the latter develop faster and are often accompanied by pain.

### Treatment

A variety of treatments have been proposed for carcinomas of the vaginal wall. External pelvic roentgentherapy should be given to every case just as it is in the treatment of carcinoma of the cervix. External roentgentherapy alone has been reported capable of sterilizing vaginal carcinomas (Courtial), but, in

### Incidence and Etiology

Cancer of the vagina is very rare being considerably less frequent than cancer of the cervix or even than cancer of the vulva. No causal factor has been incriminated for its development. The widespread use of pessaries has not resulted in a greater incidence of cancer of the vagina. Carcinoma is usually found in women 45 to 65 years old. Sarcomas of the vaginal wall are most commonly observed in girls under 6 years of age, in fact, it is generally believed that they are present at birth but not ostensible at that time. McFarland was able to collect only fifty eight cases of sarcomas of the vagina in adult women.

### Pathology

**Gross Pathology**—Carcinoma of the vagina most often develops on the upper third of the posterior wall but is also found on the lateral and anterior walls. This tumor may easily invade the rectovaginal septum and the paracystium yet actual involvement of the bladder or rectal walls has not frequently been reported. It may also secondarily invade the cervix and the vulva.

Vaginal sarcomas which occur in young girls are of the botryoid (grape like) type and arise most often on the anterior vaginal wall. The sarcoma of the adult may arise from any part of the wall and is most often of parietal rather than of mucous origin. These tumors rapidly spread to the paracystium and paraproctium, producing constriction of the bladder and rectum.

**Metastatic Spread**—Carcinomas of the vagina metastasize to the external iliac and hypogastric nodes. Inguinal node involvement is observed only after the vulva has been invaded. Sarcomas usually cause death before the development of metastatic disease. Metastases to distant viscera are rare in all vaginal tumors, with the exception of the sarcoma in the adult.

**Microscopic Pathology**—The overwhelming majority of carcinomas of the vagina are epidermoid and, as a rule are rather undifferentiated. Adenocarcinomas apparently arise from remnants of the Gartner's ducts (Novak) but adenocarcinomas of the vaginal wall are, as a general rule, secondary to primary lesions elsewhere. It has been suggested that botryoid sarcoma of the infant is in reality a mixed tumor developing from embryonal cells of the mesoderm. It presents a variable number of spindle cells in a myxomatous stroma. The sarcoma of the adult presents a highly vascular stroma and spontaneous necrosis. Melanomas of the vagina have also rarely been observed (Meigs).

### Clinical Evolution

The clinical evolution of carcinomas of the vaginal wall is very similar to that of carcinomas of the cervix. The onset is usually made apparent by vaginal discharge and a small amount of vaginal bleeding. Pain appears when extension develops to the subperitoneal areolar tissue of the parametrium or paracystium. Carcinomas of the vagina may cause wide necrotic involvement of the vulva with secondary infection and malodorous discharge. Pelvic and abdominal metastases occur, but distant blood borne metastases are exceptional.

A bloody vaginal discharge may be the first symptom of a sarcoma of the vagina, in the young girl tumor may be seen protruding through the vulva.

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## CANCER OF THE VULVA

### Anatomy

The vulva comprises the labia majora, the labia minora, the vestibule, the clitoris, and the greater vestibular glands. The labia majora are two elongated folds of slightly pigmented skin which lie medially to the inner surface of the thighs. Anteriorly, the labia majora merge to become continuous with the mons pubis while posteriorly they become narrow and terminate about 3 cm anterior to the anus. The labia minora are two smaller folds situated medially to the labia majora. The union of the labia minora anteriorly forms the anterior commissure where they divide to surround the clitoris. The clitoris is an erectile organ located just beneath the symphysis pubis (Fig 630).

The vestibule is the area extending from the clitoris to the urethral meatus and from one to the other labium majus. This triangular space also comprises the Skene's glands which end in a small orifice near the urethral meatus. The greater vestibular glands or Bartholin glands are situated on either side of the vaginal orifice in its posterolateral quadrant.

The labia majora are lined by skin with all its normal appendages, glands, and hair follicles. The labia minora are covered by squamous epithelium which is thin and moist and does not contain sweat glands or hair follicles. The vestibule is covered by the same type of mucous membrane.

**Lymphatics**—The lymphatics of the vulva are most numerous at the level of the labia majora. They gather in the direction of the mons veneris and then turn outward to end in the upper and inner group of superficial inguinal nodes. Rarely some of these lymphatics end in the lower or in the external inguinal nodes.

The lymphatics of the clitoris and of the vestibule are very variable. They follow the midline to a presymphyseal plexus, and from there the lymphatics perforate the deep fascia and terminate in the deep inguinal nodes and in the medial retrofemoral nodes (Fig 631). Another group of vestibular lymphatics follows the round ligament and empties into the lateral retrofemoral node. It must not be forgotten that the lymphatics of the vestibule may communicate with the hypogastric nodes by the intermediate of the lymphatic network of the urethra.

The lymphatics of the Bartholin glands, as most lymphatics of the region of the vulva, also end in the inguinal nodes.

general, the preliminary pelvic roentgentherapy should be complemented by intracavitary curietherapy. This treatment is best carried out by means of an especially molded apparatus made of Colombia paste which can be manipulated at a temperature that is not burning to the patient and does not melt at body temperature (Esguerra). An especially fitting apparatus with well filtered, low content radium element needles can be used for only a few hours at a time, and in this way the treatment is protracted over several weeks. Transvaginal roentgentherapy may be used to advantage in tumors which are confined to the upper half of the vagina.

The rare carcinomas of the lower third of the vagina which invade the introitus should be treated surgically in the same fashion as carcinomas of the vulva. A therapeutic inguinal dissection is often necessary and is sometimes advised as a routine procedure (Smith). In sarcomas a surgical excision should be attempted when possible but unfortunately this is seldom feasible.

### Prognosis

In the past the prognosis of carcinomas of the vagina was rather poor. With improvement of therapeutic techniques, better results have been reported each year. Moench (1931) working partly on material previously reported by Staev from the Mayo Clinic, reported on fifty three treated patients. Of twelve patients with early carcinomas treated by radiotherapy six (50 per cent) survived while only two of twelve others with early carcinoma were living following surgical treatment. Of nineteen with advanced carcinoma treated by radiotherapy one survived a total result of nine survivals (17 per cent) from two to twelve years. Tausig (1935) had two patients living five years in a series of eighteen treated with radium at the Barnard Skin and Cancer Hospital of St. Louis. Berven and Heyman (1937) reported on forty two patients treated at the Radiumhemmet of Stockholm, of whom six (14 per cent) were well five years or longer. Courtial (1938) reviewing a series of thirteen cases treated at the Radium Institute of the University of Paris found six patients living and well five or more years after radiotherapy. Smith (1940) reported a series of fifty seven carcinomas of the vagina treated by various methods at the Memorial Hospital in New York with seven patients (12 per cent) surviving over five years.

The prognosis of sarcomas is invariably poor.

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Fig. 61—Schematic drawing of the lymphatics of the vulva showing (in black) the lymphatics of the labia majora ending in the inner group of superficial inguinal nodes and superficial (in gray) the lymphatics of the clitoris and vestibule which terminate in the deep inguinal nodes and retrofemoral nodes but may have communication with the lymphatic system. (After Pouliot.)

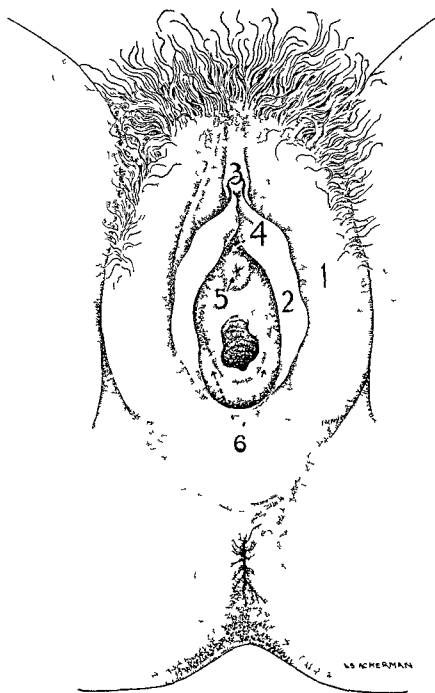


Fig 630—Schematic drawing of the vulva showing 1 labium majus labium minus 3 clitoris 4 vestibule 5 urethra 6 orifice of the Bartholin glands



are usually excavating with hard nodular borders. When the ulcerations become deep and necrotic, the underlying blood vessels may be eroded and hemorrhage may result. Leucoplakia is associated with carcinomas of the vulva in a large proportion of the cases. Taussig (1941) found associated leucoplakia in seventy-four of 107 patients with carcinoma of the vulva. The transition of leucoplakia to cancer may be very gradual, occurring in a zone either of hyperplasia or atrophy. When leucoplakia is associated with carcinoma of the vulva, multiple foci of origin may be present.



Fig 632—Early carcinoma of the labium majus near the fourchette. Note atrophy of the labia and narrowing of the introitus.

**METASTATIC SPREAD**—Nodes may be palpable in the inguinal regions. These are often tender and become rapidly fixed. Bilateral inguinal adenopathies are not unusual. Tumors arising in the vestibular area, and particularly in the clitoris, may metastasize to the hypogastric nodes. Distant spread to the retroperitoneal lymph nodes and other organs such as liver and lungs can occur.

### Incidence and Etiology

Cancer of the vulva is a postmenopausal disease which accounts for approximately 3 per cent of genital carcinomas (Schottlander). Cancer of the vulva occurs most commonly in women between 50 and 70 years of age. The peak age incidence is 60 years, but approximately 30 per cent of all patients with carcinoma of the vulva are 70 years or older. Carcinoma of the vulva is more frequent in white women than in Negroes. However, there seems to be a predominance of Negroes in the group of vestibular carcinomas. Eight of Taussig's (1941) eleven cases of vestibular carcinomas were found in Negro women.

In the history of the majority of cases of carcinoma of the vulva there is a high incidence of patients which have presented previous changes of the vulva consisting mainly of shrinkage and dryness. These changes are perhaps endocrine in nature and initiated by the menopause. The peak incidence of leucoplakia seems to be at 55 years of age, or five years earlier than the peak incidence of carcinoma of the vulva. An area of leucoplakia may have been present for some time before the appearance of carcinoma, and this leucoplakia may or may not have been associated with kraurosis. Taussig (1929) estimated that 50 per cent of all cases of vulvar leucoplakia developed into carcinoma. If this statement is correct the leucoplakia of the vulva is more of a pre-cancerous lesion than leucoplakia of the oral cavity, where the majority of the cases of leucoplakia never degenerate into carcinoma.

The pre-existing changes of the epidermis (leucoplakia) and of the dermis (kraurosis) are often found together and for this reason their simultaneous occurrence has been called leucokraurosis (Graves). Taussig designated it under the name leucoplakic vulvitis. The leucoplakia and the kraurosis however are not always associated, and in some instances each develops for a long time in the absence of the other. This fact and the none too rare incidence of vitiligo in patients with carcinoma of the vulva have led some authors into the belief of the neurotrophic origin of these lesions (Stajano).

Carcinoma which develops in the vestibular area of the vulva does not have a history of preceding leucoplakia. Trauma is definitely not an etiologic factor. Syphilitic lesions seem to play a more important role. Taussig (1941) reported on eleven patients with vestibular carcinomas nine of whom had a history of lymphogranuloma venereum in this area.

### Pathology

**Gross Pathology**—The greater majority of carcinomas of the vulva develop on the labia (Fig 632). Taussig (1940) divided 155 cases of carcinoma of the vulva into the following groups according to their point of origin:

Epidermal	104 cases
Vestibular	11 cases
Periurethral	12 cases
Bartholin gland	9 cases
Glans clitoris	2 cases
Unclassified (advanced case)	17 cases

Carcinomas of the vulva tend to spread submucosally. The large, superficial masses become later ulcerated and secondarily infected. Vestibular lesions

muscles, and connective tissue are rare. The so called hidradenoma which arises from the sweat glands is often confused with adenocarcinoma grossly. It is well circumscribed but has a tendency to ulcerate. Microscopically, hidradenomas show the evidence of their sweat gland origin with papillary-like projections and never extend beyond the basement membrane (Rothman, Novak). They are practically never malignant. One instance was reported by Eichenberg.

True basal-cell carcinomas of the vulva are very rare (Wilson). Metastatic lesions from other genital carcinomas, particularly chorioepitheliomas and carcinomas of the endometrium, have been encountered but are uncommon. Carcinoma of the cervix and rectum may directly invade the vulva, but ovarian neoplasms rarely involve it.

### Clinical Evolution

Most cases of carcinoma of the vulva are preceded or accompanied by *pruritus*. This symptom, however, is often due to the development of kraurosis and leucoplakia rather than to the carcinoma itself. The pruritus is most marked at night and at the level of the clitoris and seems to center about the clitoris and anal folds. Scratching makes further excoriation which in turn aggravates the pruritus and leads to insomnia. These symptoms may have been present for several years before the appearance of carcinoma. In addition, the kraurosis may result in shrinkage of the vaginal orifice and in marked *dyspareunia*. In some cases there is an intermittent bleeding which may become hemorrhagic.

Large plaques of leucoplakia may be present, particularly over the labia majora. They may have extended to the perianal region and to the entire vulva. Most often the leucoplakia is thin but sharply demarcated and pearly gray in color. Sometimes it is limited to the preputial folds and lower perineal region. In addition, the hair may become brittle and the skin is abnormally dry and parchment thin. Shrinkage with flattening and atrophy of the clitoris and narrowing of the vaginal orifice may have occurred (Fig 634), as well as a red mottling in the region of the labia minora on either side of the introitus.

In general, carcinomas of the vulva are papillary outgrowths which may become very extensive. Some cases, however, have a tendency to ulcerate and diffusely infiltrate and may present a large crater instead of an exophytic mass. A constant complication of carcinomas of the vulva is the presence of secondary infection which may be more or less marked, depending on the case. In uncontrolled cases, the patients rapidly become cachectic and may die as a consequence of complications rather than because of generalization of the disease. Diffuse cellulitis and phlebitis are not uncommon complications.

The involvement of the inguinal nodes occurs rather early in the development of the disease. These nodes, however, may also be enlarged because of secondary infection.

### Diagnosis

The history and physical findings in carcinomas of the vulva make the clinical diagnosis rather simple. However, a few other conditions might offer a problem of differential diagnosis. Benign lesions such as *condyloma* usually occur in young women. These are soft, nonulcerated papillary outgrowths which

**Microscopic Pathology**—Carcinomas of the vulva are squamous in nature with the exception of Bartholin gland carcinomas and some of those developing in the vestibule which may be adenocarcinomas. Most of the carcinomas arising from the labia are rather well differentiated but those which arise from the clitoris and vestibular region usually are not.

The microscopic picture of leucoplakia often shows acanthosis, hyperplasia of the epithelium with papillary downgrowth and fairly prominent chronic inflammation. In the later stages atrophy of the epithelium occurs, skin appendages disappear, the elastic tissue becomes reduced in amount, and there are focal areas of hyalinization of the collagen. Carcinomas arising from leucoplakia occur most commonly in areas of atrophy.

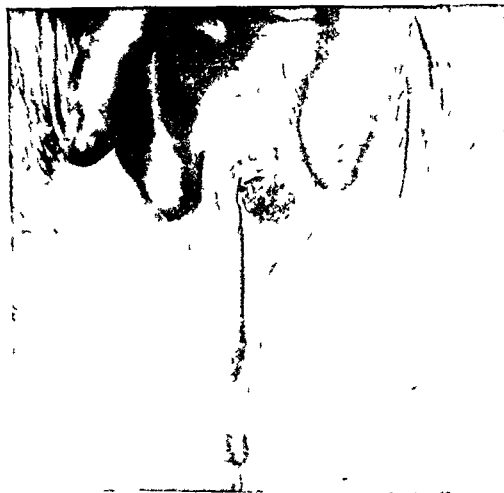


Fig. 622.—Early differentiated carcinoma of the vulva (see general atrophy of the labia).

Bowen's disease may also be present, showing hyperplasia, disorderly pattern of the architecture, numerous mitotic figures, and foam cells (leffcoite). The basement membrane, however, remains intact in Bowen's disease, the carcinoma remaining strictly intraepidermal. This situation may not remain as such and the carcinoma may transgress through the basement membrane.

Melanocarcinomas of the vulva are relatively infrequent. They usually arise from a pre-existing nevus. Pigment tumors arising from the blood vessels

made clinically and will be confirmed by biopsy. When the inguinal nodes are enlarged and have reached a size over 3 cm in diameter, they are invariably metastatic. This, however, should always be confirmed by aspiration biopsy. Smaller nodes about 1 cm in diameter are usually only inflammatory.

### Treatment

As it has been noted by Taussig, a large percentage of cases of leucoplakia of the vulva will inevitably end in carcinoma. For this reason, prophylactic treatment of leucoplakia of the vulva is of true value. Such treatment consists in local excision of leucoplakic areas, but in general a vulvectomy is more satisfactory and avoids recurrences of the leucoplakia. This preventive surgical measure is accompanied by a very low operative mortality. Intensive treatment of venereal lesions of the vulva is also a preventive measure.

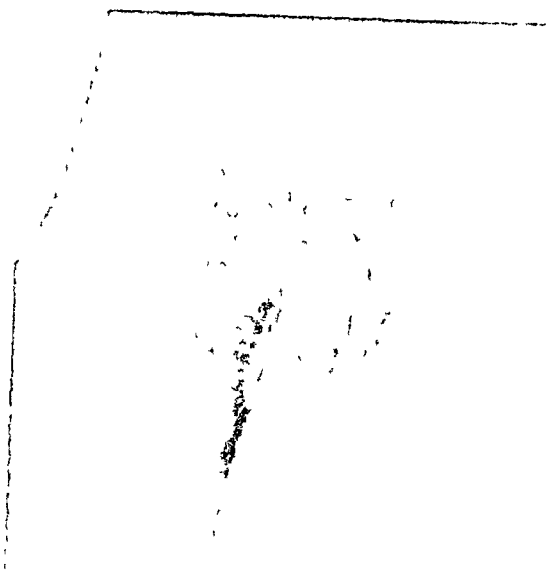


Fig. 635.—Typical condyloma of the vulva spreading over both labia majora and presenting no ulceration. (Courtesy of Dr. F. O. Fliche, Homer Phillips Hospital, St. Louis, Mo.)

**RADIOTHERAPY**—Most vulvar tumors are rather radiosensitive and could successfully be treated by means of roentgentherapy directed to a perineal field or by interstitial implantation of radium needles. However, the necessary dosage for the total sterilization of these tumors usually implies damage to the surrounding skin. The skin of the vulva is normally more sensitive to radiations than is the skin of other areas. In addition, the underlying dystrophies which are almost constantly present in these old patients will usually lead to marked changes and resulting radionecrosis. These untoward effects do not necessarily follow

become pedunculated (Fig 635) and are usually associated with other venereal diseases. *Lymphogranuloma venereum* is often also associated with rectal lesions and may be ruled out because of a positive Frei test. However, it should not be forgotten that this, as any other venereal disease, is compatible with a concomitant carcinoma of the vulva. Other benign tumors such as hemangiomas, leiomyomas, lipomas, and fibromas are very rare in the vulva. They are easily



Fig 634—Leucoplakia of the vestibular region of the vulva with atrophy of the clitoris and marked narrowing of the vaginal orifice.

differentiated because of the absence of ulceration or infiltration and because of the slow rate of their growth. The *hidradenoma* of sweat gland origin is a well circumscribed lesion usually of long duration. When it becomes ulcerated it may be confused with carcinoma, but the biopsy will be conclusive.

*Melanocarcinomas* of the vulva are also rare. They usually arise from a pre existing nevus. The diagnosis may be made on the basis of accelerated rate of growth and extension of the area of pigmentation. Diagnosis will be easily

electrocoagulation of the primary lesion and seems to have had no difficulty in subsequent healing of these areas. However, this procedure is unquestionably less satisfactory if one considers only the long period of healing which will be necessary.

A prophylactic bilateral inguinal dissection does not seem a worth-while risk in the majority of these aged patients. In Taussig's (1940) series, the percentage of the five year results of vulvectomy followed by inguinal dissection was not considerably better in the patients without inguinal metastases (fourteen



Fig. 637—Advanced malignant melanoma of the vulva

of twenty-two) as compared with those who showed definite lymph node metastases (ten of nineteen). On the contrary, when this operation is applied to the treatment of inguinal nodes which are already clinically evident, it offers the patient an unquestionable added advantage. Taussig (1940) demonstrated the advantage of an enlarged bilateral inguinal dissection following vulvectomy. He advocated the Basset operation which dissects the nodes of both inguinal regions, and, in addition, extirpates external iliac, internal iliac, and obturator nodes. This enlarged operation is technically difficult and probably often incomplete. It is reasonable to expect that when the higher nodes are involved,

the application of radiations, but their chances of development are greater here than in other areas. Radiotherapy is able to control a small percentage of these cases, but, in general, surgical treatment contributes better results with much less discomfort and fewer complications. It should not be forgotten, however, that whenever surgery is contraindicated, the patient may be offered some chance of cure by careful administration of radiotherapy.



Fig 636 —Advanced ulcerating carcinoma of the vulva

**SURGERY** —The surgical excision of carcinomas of the vulva is generally accepted as the most satisfactory form of treatment. This treatment has the advantage that in cases of accompanying leucoplakia the excision will include all other potentially carcinomatous areas. In general vulvectomy should also include a large area of all perineal skin. Taussig (1936) reported on five patients in whom a new carcinoma had developed in a series of forty patients in whom islands of leucoplakia were not excised. Berven recommends wide



## Chapter XV

# CANCER OF THE MAMMARY GLAND

### Anatomy

The mammary glands lie directly over the pectoralis major muscles from the second to the sixth rib anteriorly and from the sternum to the anterior axillary line. They have the aspect of a hemisphere in the middle of which there is a salient papilla the nipple surrounded by an area of pigmented skin called the areola.

The mammary gland is made up of twelve to twenty glandular lobes, each one with a ramified duct. These ducts are irregular and tortuous and travel in the direction of the nipple. Close to the nipple they dilate to form the ampullae and then divide into minute ducts which finally end in small openings in the nipple. The ducts and acini have two layers of fibrous covering, an inner periductal or periacinar, and an outer the perilobular connective tissue. The cells of the acini are cuboid in shape while those of the lactiferous ducts are columnar. The covering of the gland is made up of fibrous tissue or fascia which is continuous with the fibrous tissue overlying the pectoralis major. From the inner lacis of the fascia, strands or septa extend inwardly to separate the gland into its different lobes. The gland is encased in a layer of fat except in the region of the nipple and areola. Posteriorly this fatty stroma forms a simple cushion for the gland.

Supernumerary breasts with or without the corresponding nipples are observed most frequently below and inside the breast overlying the pectoralis major at the anterior axillary line or in the axilla.

**Lymphatics**—The lymphatics of the skin of the breast form a dense network under the areola. This network is continuous with the lymphatics of the skin of the surrounding regions forming an uninterrupted network over the entire surface of the chest, neck and abdomen. Thus the lymphatics of the skin of one breast communicate with the lymphatics of the skin of the opposite breast. In addition some lymphatic trunks originating in the skin may cross the midline and drain into the axillary nodes of the opposite side (Oelsner).

The lymphatics of the mammary gland rise from the inter- or perilobular spaces. Some follow the ducts and end in the subareolar network of lymphatics of the skin but the majority originate in the base of the breast and travel toward the axillary lymph nodes. Others end in the internal mammary chain and still others on the transverse cervical chain of lymph nodes (Rouvière). The lymphatics of glandular origin may follow these pathways.

(1) The *axillary or principal pathway* is formed by several trunks coming from the upper and lower half of the gland passing through the fascia, and ending in the external mammary chain of nodes situated between the second

the disease may also have gone further along and consequently the operation is not justified. In general, a thorough bilateral inguinal dissection will be satisfactory.

### Prognosis

Carcinoma of the vulva has a relatively favorable prognosis second only to carcinoma of the endometrium in tumors of the female genital organs. Taussig (1910) reported thirty one five year survivals (42 per cent) of a group of seventy four patients who were surgically treated. In Taussig's (1940) series forty one patients had a local excision of the primary tumor and, in addition, an enlarged bilateral inguinal dissection. Twenty four of these patients (58 per cent) remained well five years after treatment. Berven reported on sixty five patients (36 per cent) who survived five years after treatment in a group of 177 patients. In Berven's series there were eighty one patients without inguinal metastasis. Forty eight of these (60 per cent) remained well five years after treatment.

Carcinomas of the vestibular area of the vulva have a poorer prognosis than those arising from the labia. The dimensions of the primary lesion and the duration of its presence also have a bearing on the prognosis. The larger the tumor and the longer it has been present, the greater the possibilities of intra abdominal metastasis.

When a surgical excision of the primary lesion and a bilateral inguinal dissection are not possible, the radiotherapeutic methods may still offer the patient some chances of survival. Berven reported 13 per cent five year survivals with the use of radiotherapy.

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and third intercostal spaces. Some of these lymphatics, however, do not stop in these nodes but follow directly to the group of nodes of the axillary vein or to a central group of nodes in the axilla (Fig 638)

(2) The *transpectoral pathway* is formed by the lymphatics that pass through the pectoralis major with the branches of the lateral thoracic artery and end in the supraclavicular lymph nodes. Some of these may follow the inferior borders of the pectoralis major and ascend directly to the infraclavicular lymph nodes behind the pectoralis minor or between the two pectoral muscles. In this last instance they may be interrupted by a few interpectoral lymph nodes.

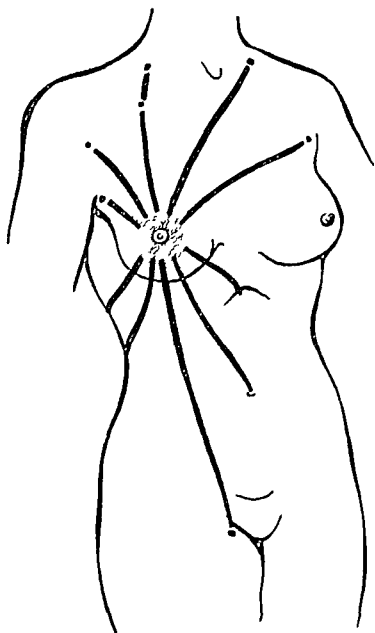


Fig 639—Diagrammatic sketch of the cutaneous lymphatics of the breast leading from the subareolar network to the axillary and supraclavicular lymph nodes on both sides and through widespread cutaneous anastomosis, to the dorsolumbar and abdominal regions as well as to the inguinal lymph nodes. (From Ducuing J. *Précis de cancérologie*. Paris, 1932. Masson & Cie.)

(3) The *internal mammary pathway* runs toward the midline, passes through the pectoralis major and the intercostal muscles, usually close to the sternum, and ends in the nodes of the internal mammary chain.

The lymphatics originating in the mammary gland also follow an alternate lateral pathway (Rouvière) and end in the lymph nodes of the opposite axilla.

### Incidence

In 1940, Dorn estimated that cancer of the breast made up 26 per cent or over one in every four cases of cancer in white women. In 1942, Pfahler wrote, "approximately 50,000 women in the United States have cancer of the

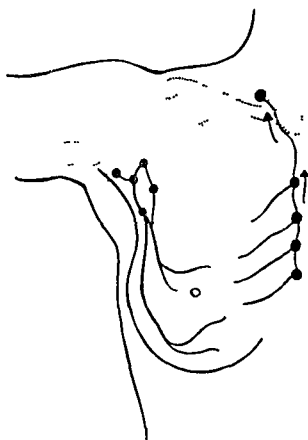


Fig 638—Anatomic sketch of the lymphatics of the breast leading to nodes of the axilla  
internal mammary chain and supraclavicular areas

women who had ceased menstruating (Table LVII) Geschickter has suggested that the menopause is probably delayed in a great number of patients with carcinoma of the breast, but 63 per cent of our patients with carcinoma of the breast had ceased menstruating before the age of 50 years

TABLE LVII COMPARISON OF CARCINOMA OF CERVIX, ENDOMETRIUM, AND BLAST IN RELATION TO RACE DISTRIBUTION AND INCIDENCE BEFORE OR AFTER CESSATION OF MENSTRUATION (THIS ISRAELI STATE CANCER HOSPITAL)

	TOTAL NUMBER OF CASES*	BEFORE CESSATION OF MENSES	AFTER CESSATION OF MENSES	PROPORTION OF WHITE PATIENTS	PROPORTION OF NEGRO PATIENTS
Carcinoma of the cervix	131	50%	50%	90%	10%
Carcinoma of the breast	416	20%	80%	92%	8%
Carcinoma of the endo- metrium	94	7%	93%	95%	5%

\*Only those cases with suitable data are included. Percentages are rounded for clarity

There is about one case of carcinoma of the male breast for every 100 cases in women. *Sarcomas* make up between 0.5 and 3 per cent of all malignant tumors of the breast. They occur at any age after puberty but are found most frequently in patients in the fifth decade of life.

### Etiology

It is tempting to draw parallels between the findings in laboratory animals and the human cancer of the breast (see *Cancer Research*, page 36). Wood recently followed and reported a family, several members of which developed bilateral carcinoma of the breast. In the third generation studied, there were three sisters, all of whom had carcinoma of the breast, one developing the disease at the age of 18 years. In all cases examined, the mammary glandular tissue showed changes suggesting hyperestrogenism. It is known that carcinoma of the breast occurs more frequently in women without children and in mothers with a history of abnormal lactation.

As a result of experimental work on animals, a great deal has been written on the question of whether the injudicious clinical use of estrogens can have anything to do with the production of carcinoma of the breast in women. There are very few cases in the literature to support such a thesis (Auchincloss, Parsons, Waggoner). Whether the clinical administration of estrogen can be the cause of carcinoma in a breast is still questionable. It is possible that the administration of estrogens is dangerous in patients with a family history of cancer of the breast.

**Chronic Cystic Mastitis**—The relation of chronic cystic mastitis to carcinoma of the breast has been written about voluminously. In the literature, its reported association with cancer varies from very small percentages to 100 per cent. However, a critical analysis of the pathologic criteria reveals that the percentages reported are proportional to the liberality of the pathologist in diagnosing such a lesion. If one omits lesions due to degenerative phenomena, and also obvious lesions which have not been shown to bear

breast at the present time" It has the highest prevalence rate of all forms of cancer in white women

It is difficult to estimate the morbidity rate of cancer of the breast Levin, however, in studying the comparative morbidity rates in upper New York State for 1942 found five living patients with cancer of the breast for each death from cancer of the breast

The mortality rate for cancer of the breast in the United States has been increasing steadily and alarmingly since the beginning of the century

YEAR	DEATHS	POPULATION
1920	6 663	103 710 620
1930	10 912	122 775 000
1940	15 488	131 609 753

These statistics show that in the past twenty years there has been a 58 per cent increase in the mortality rate

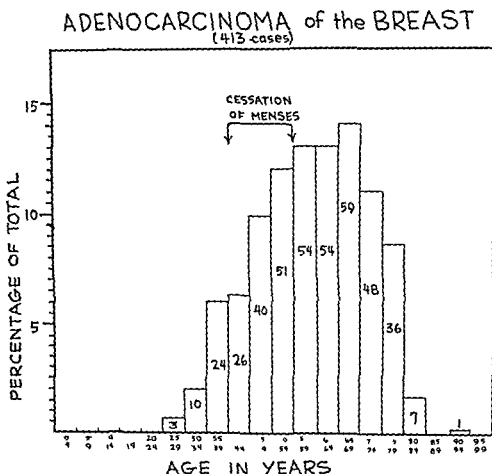


Fig 640—Age distribution of 413 patients with carcinoma of the breast admitted to the Ellis Fischel State Cancer Hospital from 1940 to 1946

The peak age incidence is usually reported to be 45 to 49 years of age. Few cases have been reported in patients 20 to 25 years old. Of 413 patients admitted to the Ellis Fischel State Cancer Hospital during its first six years only three were under 30 years of age, and one half of the patients were 50 to 69 years old (Fig 640). The majority of these tumors were found in

are known. The specimen should be oriented, the tumor located, and the condition of the nipple noted, as well as the presence or absence of ulceration and edema of the skin overlying the tumor. Dissection should start with the nipple, using care to ascertain whether or not the main ducts are dilated and whether or not tumor is arising from or involving that area. The primary tumor should be measured in three dimensions and its relation to skin, nipple, pectoral fascia, and quadrants of the breast given. Step sections should be made of the tumor, including the overlying skin, and the individual characteristics observed. Other sections should be made of the transition points between apparently uninvolved breast tissue and the diseased area. If the tumor arises in proximity to the nipple or has extended to involve the pectoral fascia, appropriate sections of these areas should be selected. Multiple sections should be taken from the other three quadrants of the breast where the parenchyma is most prominent.

At the time of operation, the high point of the axilla should be tagged. Later, at gross examination, this will facilitate division of the axilla into high, mid, and low portions. Lymph nodes obtained from these areas should be kept separately so that the extent of axillary involvement can be ascertained microscopically. Inconstant nodes located between the pectoral muscles should always be looked for, as they may be the only ones involved. In our experience, nodes are most easily found by palpating small amounts of axillary fat against a strong light. By this means, nodes only 5 mm in diameter may be seen as fairly distinct gray nodules, well delineated against the translucent background.

*All nodes must be sectioned.* If examination of the axilla is rushed, only a small fraction of the existing nodes will be found. We have seen numerous instances in which only one of twenty-five or thirty nodes was involved by carcinoma, but these cases were and should be classified as having axillary involvement. An average of between twenty and thirty nodes should be found in every axillary specimen. As many as eighty nodes have been studied in one case. *Incomplete examination of the axillary area after radical mastectomy is probably one of the main reasons why statistics on this subject vary so greatly.* While this search for nodes is time consuming, the information so obtained is valuable enough to warrant it.

The gross appearance of the nodes varies with the presence or absence of tumor and of inflammation. If the nodes are negative with no inflammation they are often small, soft, and consequently difficult to find. On section they are homogeneous, gray in color, and infrequently give cause for error. When the primary tumor is ulcerated and inflamed, then the axillary nodes are enlarged and hard, even though they may not contain carcinoma. Sharply delineated grayish-yellow areas within nodes almost certainly represent metastatic carcinoma.

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Muir has emphasized that a great percentage of carcinomas of the breast arise from duct epithelium. Probably about 5 per cent arise from acinar epithelium (Foote and Stewart). In many cases the tumor is advanced, and consequently the exact histogenesis is obscured. The form which a carcinoma

any definite relation to cancer such as fat necrosis, fibroadenomas, periductal mastitis, then the frequency of association of so called chronic cystic mastitis and carcinoma drops sharply. In a group of 967 mammary carcinomas, MacCarty found 100 per cent to be associated with chronic cystic mastitis. Semb, in 140 cases of carcinoma of the breast, reported fibroadenomatosis present in 80 per cent. His determinations, however, as Foote and Stewart pointed out, were made without regard to menstrual changes. In 300 cases of mammary carcinoma studied by Foote and Stewart, 59 per cent presented at least one of five proliferative changes (cysts, duct papillomatosis, blunt duct adenosis, sclerosing adenosis, apocrine epithelium), 35 per cent presented two or more, and 17 per cent presented three or more.

It would be valuable, as Foote and Stewart stated, if the anatomic development of cancer from one of these proliferative benign breast lesions could be shown in every case. Unfortunately almost all carcinomas of the breast available for pathologic study are so advanced that the exact point of origin is obscured by the pathology present. At times transitions of this type can be observed in early carcinomas. Foote and Stewart saw cancer arising in duct papillomatosis both in single and multiple cysts, apocrine type epithelium, and in blunt duct adenosis.

The incidence of so called chronic cystic mastitis in women over 30 years is yet to be reported with an accurate enumeration of the pathologic criteria. Foote and Stewart, on the basis of an examination of fifty-four patients, indicated that the incidence of chronic cystic mastitis in the general population would be low. Warren (1940) also implied that there was a low incidence of chronic cystic mastitis in the female population.

If a patient has chronic cystic mastitis, does that patient have any greater chance of developing carcinoma of the breast than one who does not? The best studies are those based on a careful pathologic study of a large group of patients in whom portions of the breast have been removed for chronic cystic mastitis. Such a study was made by Warren who continued follow-up on 1206 patients with chronic cystic mastitis. Cancer developed in forty-two. This is about three times the normal incidence. Warren concluded that the incidence of carcinoma of the breast in women 30 to 49 years old with chronic mastitis and related lesions is about twelve times greater than the general incidence in the female population of Massachusetts.

*There is apparently no doubt that carcinoma of the breast is associated in a much higher incidence than one could statistically expect it to be with the proliferative lesions of chronic cystic mastitis. There is also no doubt that occasionally these proliferative lesions are the beginning point of cancer.*

### Pathology

**Gross and Microscopic Pathology**—It is of utmost importance that the surgical specimen of a radical mastectomy be so sectioned and so studied that when the examination is completed the extent of the tumor, the character of its local invasion, the distribution of its metastases (and thereby its prognosis)



the dense background of almost cartilaginous stroma. In fact, if the tumor has been present for many years even areas of calcification may be present. Not infrequently there are areas of chronic cystic mastitis either intimately associated with or distinct from the tumor.

Within the breast, the carcinoma spreads with a variable rate of growth. With increase in size, ramifying fingers of tumor extend out into the breast parenchyma. The main tumor mass may enlarge to involve the skin which becomes thin, taut and finally ulcerates. The tumor may also extend downward to the pectoral fascia which for a time, restrains its extension. After growth through the pectoral fascia the tumor becomes fixed and further extension may involve the pectoral muscles. In advanced disease, when the tumor approximates the axilla, it may directly invade it, and the tumor and axillary masses become continuous and fixed.

The microscopic appearance of carcinoma of the breast of the most common type can vary considerably. In many instances the duct origin can be traced. The cellular nature of the tumor often varies in different areas. In the large tumors, zones of necrosis and hemorrhage are common. The amount of connective tissue stroma present is extremely variable and on the age of this connective tissue will depend its relative cellularity. Of considerable importance is how the tumor appears under low power. The well-differentiated lesions have a fairly orderly pattern with some tendency toward adenoid formation. The undifferentiated carcinomas have an extremely disorderly pattern, marked variation in cell size and shape and innumerable mitotic figures, many of which are abnormal.

In *Paget's disease* there is a weeping eczematoid lesion involving the nipple, areola and occasionally a large area of contiguous skin. On section, definite carcinoma is found directly beneath the nipple. The disease is often poorly circumscribed but very hard because of increased connective tissue. The tumor has chalky yellow streaks and is usually confined to the ducts.

The microscopic examination always shows the presence of intraductal carcinoma. Muir reports that intraductal carcinoma was present in the nipple alone in all of his thirty-nine patients, in the breast and nipple in thirty-four, and was accompanied by infiltrating carcinoma of the breast in thirty. Cells present in the ducts are also present in the overlying epidermis (Fig 655). These cells are malignant, arise from duct epithelium, and directly invade the nipple. This invasion of the contiguous epithelium is what gives the clinical appearance of *Paget's disease* (Fig 654). Spread to the overlying skin probably occurs because of the migration of these cells. If enough sections are made communication between duct carcinoma and tumor cells growing in the overlying epithelium can always be demonstrated. It is probable that the carcinoma arises within the ducts and moves toward the nipple rather than the converse.

*Comedo carcinoma* is often quite large, not infrequently has ulcerated through the skin and is accompanied by evidence of infection. On cut section the tumor shows well-demarcated plugs of carcinoma within dilated ducts (Fig 641). However, these plugs may spread diffusely and give an impression of

takes depends largely on whether the tumor arises from duct or acinar epithelium, whether it is confined to the ducts by dense connective tissue, whether it produces large amounts of mucin, or whether it arises within a cyst. Undoubtedly, hormonal influences play some role in the pathologic form, and such influences apparently act unequally on various portions of the breast. The tumor may remain localized in the ducts for months or even years, depending on the ability of the connective and elastic tissue to prevent spread into the breast parenchyma. In the older age groups when atrophy of the breast parenchyma has taken place, the tumor arises from duct epithelium. In the younger age groups in which acinar tissue is prominent and where the tumor is more frequently undifferentiated the neoplasm can arise from acinar epithelium and spread quickly over a wide area. The tumor also grows rapidly during pregnancy and lactation because of increased vascularization and perhaps also because of other unknown factors.

The grading of carcinomas of the breast in the main is not satisfactory because the great majority of carcinomas fall into an indeterminate group, and for this reason attempts at segregation of carcinoma in various grades are generally disappointing (Warren 1943). The presence of fibrosis hyaline, lymphocytic infiltration, and calcification has nothing to do with the grading of the tumor (Hargensen, 1933). It is true that a relatively small proportion of carcinomas of the breast have an extremely disorderly pattern, show marked variation in size and shape of cells, tumor giant cells, and often have bizarre mitotic figures. On the other hand, there are also a few extremely well differentiated carcinomas which have a very orderly pattern and a tendency toward adenoid arrangement.

The classification of carcinoma of the breast is still somewhat unsatisfactory. It is worth while to classify them, however not only from a pathologic sense but also from the clinical appearance. Table LVIII is a tentative classification of carcinoma of the breast.

TABLE LVIII TENTATIVE CLASSIFICATION OF CARCINOMAS OF BREAST (THIS AS WELL AS OTHER CLASSIFICATIONS HAS DISADVANTAGE THAT MOST CASES FALL INTO AN INDETERMINATE GROUP)

	RELATIVE INCIDENCE
Arising from duct epithelium	
Carcinoma (no specific type)	Over 80 per cent
Carcinoma plus Paget's disease	About 2 per cent
Comedo carcinoma	About 4 per cent
Acute carcinoma (inflammatory)	Less than 5 per cent
Capillary or adenocarcinoma	Less than 5 per cent
Mucinous carcinoma	About 1 per cent
Epidermoid carcinoma	Less than 1 per cent
Arising from acinar epithelium	
Lobular carcinoma	Approximately 5 per cent

In the common type of carcinoma of the breast the findings on section may be somewhat variable. If the tumor is soft, cellular, with little stroma then areas of recent and old hemorrhage may be present. Much more frequently, however, the tumor is hard with poorly defined chalky yellow areas seen against

irregular nodularity in the breast. On compressing the breast, wormlike masses of tumor can be extruded from the involved ducts. In a few isolated areas, invasion of the surrounding breast tissue may have occurred. The comedo carcinoma usually shows well-differentiated tumor cells confined to the ducts. It is not infrequent for these ducts to be greatly distended by the tumor, and it is common to see considerable thickening of their walls (Fig. 642). This thickening is due to connective tissue production, and elastic tissue stains often show very large amounts of it. This particular quality of the comedo carcinoma is unexplained, but the tendency of the connective and elastic tissues to wall in the tumor no doubt explains its gross and microscopic appearance. In some of these tumors, breakthrough occurs and a typical infiltrating carcinoma of duct-epithelial origin is observed.



Fig. 642 - Large pseudocystic papillary comedocarcinoma of the breast.

The acute or inflammatory carcinoma invariably shows a diffuse edema of the overlying skin much larger than the localized tumor. Ulceration is practically never present. The tumor is frequently fairly diffuse within the breast parenchyma. The axillary nodes are invariably involved. This type of carcinoma is usually extremely undifferentiated, often associated with inflammatory cells. Most important, however, there is usually widespread involvement of the subdermal lymphatics together with hyperemia of the subpapillary plexus. These changes account for the edema and erythema of the overlying skin.



Fig 641.—Gross specimen of comedo type of carcinoma of the breast. Note nodular comedon-like rings of carcinoma within the ducts.

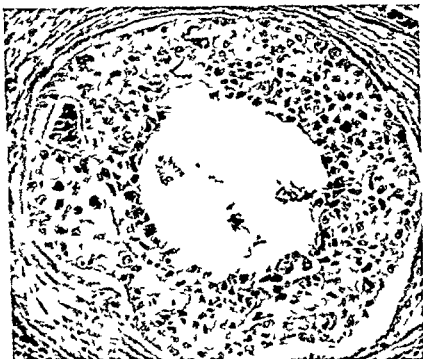


Fig 64.—Photomicrograph of comedo type of carcinoma of the breast showing variation in size and shape of cells with confinement within the thick walled ducts (moderate enlargement).



Fig. 645—Mucinous carcinoma of the breast having a gelatinous like quality



Fig. 646—Photomicrograph of mucinous carcinoma of the breast Nests of tumor cells floating in a sea of mucus

*Papillary cystadenocarcinomas* arise in some instances from pre existing intraductal papillomas and usually present well delineated cystic masses. On section areas of hemorrhage are often present and the tumors have of necessity transgressed the wall of the cyst in many instances growing over a wide area beneath the overlying skin. The papillary cystadenocarcinoma is made up of papillary projections with layering of the epithelium, associated hemorrhage, increased vascularity, and growth of the tumor through the surrounding connective tissue wall of the cyst (Figs 643 and 644)



Fig 644 — Well-defined adenocarcinoma of the breast (moderate enlargement)

The *mucinous carcinoma* is usually quite large when first seen. On palpation it feels somewhat cystic and on section frequently appears circumscribed and encapsulated. The mucin may dominate the gross appearance and it may have a current jelly gelatinous glistening glassy appearance (Fig 645). This may be patchy in distribution or may cover the whole surface. The tumor varies in color from purple to reddish brown to gray. In the mucinous carcinoma the amount of mucin present in different stages is variable. Not too infrequently only small nests of cells are present in large masses of acellular mucin (Fig 646). The theory that the mucin is a product of the cell rather than of the stroma is supported by its presence in the metastases to lymph nodes and to areas where connective tissue is sparse. Mucin may distend the cells so that they have a signet ring appearance similar to that seen in some carcinomas of the stomach. When this appearance is present, growth is very rapid. This type usually shows well preserved mucin secreting cells (Squamous).

*Epidermoid carcinoma* is very rare and is usually far advanced when first seen. When found it is frequently in a Negro patient. On section the tumors usually give evidence of origin from duct epithelium. An epidermoid



Fig. 648 —Photomicrograph demonstrating the origin of a cystosarcoma phyllodes from a pre-existing intracanalicular adenofibroma (low-power enlargement) (From Cooper, W. G. and Ackerman L. V. Surg. Gynec. & Obst. 1943)



Fig. 649 —Photomicrograph of a cystosarcoma of the breast. Note tumor cells growing beneath intact overlying epithelium (low-power enlargement) (From Cooper, W. B. and Ackerman L. V. Surg. Gynec. & Obst. 1943)

carcinoma arising from duct epithelium is a pathologic curiosity (Foot). We have seen only two cases in 413 consecutive breast carcinomas. The gradual metaplasia of this epithelium to well differentiated squamous epithelium can usually be traced. These tumors have the histologic appearance of a squamous carcinoma form epithelial pearls and intercellular bridges, and have the characteristics of epidermoid carcinomas elsewhere. Very rarely, epidermoid carcinomas can follow squamous metaplasia in a pre-existing fibroadenoma (Geschickter).

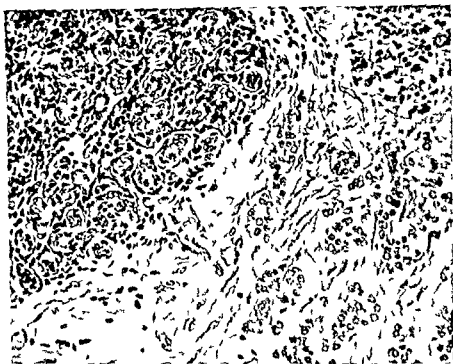


Fig. 647.—Photomicrograph of a lobular carcinoma of acinar origin. Note tumor growing around a prominent lobule.

Lobular carcinomas are relatively infrequent, often forming a diffuse mass within the breast. At times it is difficult to see any abnormality except what appears to be very large lobules. There are no chalky streaks present. After infiltration develops it assumes the characteristics of any mammary carcinoma (Foot and Stewart). The lobular carcinoma follows a distinct pattern. In a lobule or in a group of lobules there may be increased numbers of cells with a disorderly pattern and usually with a few mitoses. Occasionally there are small zones of necrosis and as the process continues more and more lobules become involved until microscopically there is invasion of the parenchyma (Fig. 647). It apparently has multiple foci of origin.

Sarcomas of the breast are of two main varieties, the most common arising from a pre-existing pericanalicular or intracanalicular adenofibroma, and the other arising from the interlobar and interlobular fibrous tissue. The first variant designated as *cystosarcoma phyllodes*, usually becomes very large. On section it may present a frondlike appearance with numerous clefts, cystlike



involved nodes and begins growing in the loose fat of the axilla, and finally, tumor in the axilla becomes so advanced that fixation occurs. At times the metastases to the axilla are restricted to a single large node which may even reach a diameter of 5 centimeters. In relatively few instances the axillary node groups will be by-passed, and the first nodes involved will be those of the infraclavicular or supraclavicular areas. It is also not too rare for the nodes of the anterior mediastinum or even the opposite axilla to be involved. These metastatic lesions occur particularly from tumors located in the inner quadrants of the breast.

After regional lymph node involvement, the lungs and pleura are commonly implicated. Tumor spreads directly to the pleura through the lymphatics which travel by the internal mammary chain. With pleural involvement, the lymphatics are widely invaded and this process takes on all the characteristics of lymphangitic metastases. The liver and bones may also become involved. The dorsal spine may even be involved without lung metastases because of spread through the vertebral vein plexus. These metastases within the vertebrae, pelvis, and skull (sites of predilection) are almost invariably osteolytic in type. Involvement of other organs such as the suprarenal glands, ovaries, and spleen is not unusual.

Cystosarcomas of the breast only rarely metastasize to the axillary lymph nodes (Cooper). Fibrosarcomas, however, much more commonly metastasize, particularly to lungs, liver, and brain.

### Clinical Evolution

There are very few early symptoms of carcinoma of the breast. The most important single presenting sign is a lump, usually painless. Infrequently, the first symptom is a large mass in the axilla or a sensation of heaviness in the breast, or there may be pain due to metastases to the vertebrae (Table LIX).

TABLE LIX RELATIVE FREQUENCY OF COMMON CLINICAL SYMPTOMS AND SIGNS IN 100 CONSECUTIVE PATIENTS WITH CANCER OF THE MAMMARY GLAND

SYMPTOM	ORDER OF APPEARANCE			FREQUENCY
	FIRST SYMPTOM	SECOND SYMPTOM	THIRD SYMPTOM	
Lump	78	9	1	88
Local pain	12	28	8	48
Enlargement of lump		16	4	20
Lump in axilla	4	5	1	10
Soreness of nipple	6	2		8
Discharge from nipple	4	2	2	8
Retraction of nipple	1	5	2	8
Ulceration		5		5
Enlargement of breast	1			1
Attachment to skin		2		2
Weight loss			5	5
Hemorrhage			1	1

The rate of growth of the tumor is extremely variable, some tumors growing rapidly, others taking several years to reach any appreciable size. With increase in size of the tumor, the overlying skin may become thin and edema and local

spaces zones of hemorrhage and mucinous degeneration. The cystosarcoma phyllodes usually remains well localized, but, after many months of growth, can eventually rupture through the skin and on rare occasions, may invade the underlying muscle. It nearly always exhibits some area which suggests its origin from the stroma of a pre-existing adenofibroma (Fig 648). The epithelial elements play only a passive role.

The fibrosarcomas are usually well circumscribed, firm and grayish white in color and often reveal zones of necrosis and hemorrhage (Fig 650). These sarcomas do not as a rule, cause nipple retraction or skin involvement. The fibrosarcoma has a much greater tendency toward local invasive growth. The typical fibrosarcoma arising from connective tissue shows cells varying from well differentiated to extremely undifferentiated, and tumor giant cells are often present. These sarcomas may show cartilage or bone and for that reason are called chondro or osteogenic sarcomas but there is no justification for such a nomenclature. The connective tissue is the primary source of the tumor.

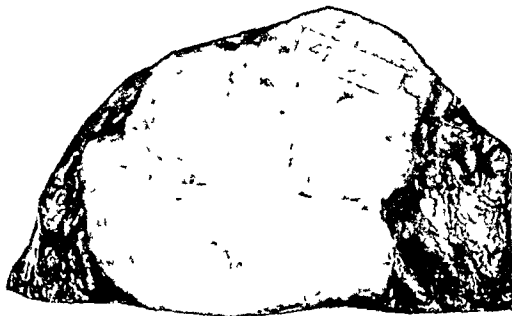


FIG. 650.—Well circumscribed homogeneous fibrosarcoma of the breast.

Sarcomas arising from other components of breast tissue are pathologic curiosities. Liposarcoma, lymphosarcoma, myosarcoma, and hemangioendotheliomas can rarely appear (Hill, Adair). Lymphosarcomas may occur within the breast as a part of the generalized process or they may be localized within the breast parenchyma. Melanocarcinomas in the breast are undoubtedly not primary but occur either as metastases or as an extension from a melanocarcinoma arising in the overlying epithelium. Hodgkin's disease of the breast has been reported (Adair). Carcinosarcoma is a doubtful entity.

**Metastatic Spread.**—Involvement of the axilla by carcinoma develops in three stages: first, tumor reaches the axillary lymph nodes by emboli and gradually fills up a node or nodes; second, it breaks through the capsule of these

*Comedo carcinoma* is relatively infrequent, making up only about 4 per cent of all breast cancers. It has two peak age incidences, one between 40 and 45 years and the other between 50 and 54 years (Geschickter). It apparently occurs more frequently in those patients with a pre-existing mammary dysplasia than in those with no previous history. These patients give a long history of a slowly growing tumor often accompanied by discharge from the nipple. The tumor feels fairly firm and often grows just beneath the thinned-out overlying



Fig. 652—Advanced carcinoma of the breast with ulcerated skin nodules, diffuse infiltration and fixation.

skin. Dimpling of the skin or retraction of the nipple are rare, however. After the growth reaches a large size, it may ulcerate through the skin, and infection with bleeding from the tumor may take place. With ulceration the nodes may increase in size because of infection. In spite of the large size of the tumor and the long duration, axillary node involvement is infrequent.

*Inflammatory carcinoma* of the breast is a relatively rare form of mammary cancer. According to Taylor, it has two forms, a primary and a secondary. In the primary form, the changes occur where a lump has been present for some

pain appear. Satellite skin nodules may develop around the tumor. If the tumor metastasizes to the axilla and the nodes become fixed (Fig. 651), edema of the arm may be noticed. With further growth of the tumor, ulceration of the skin may occur (Fig. 652), and with ulceration there may be hemorrhage and infection. Weight loss and the development of secondary anemia usually follow.



FIG. 651.—Large fixed axillary metastasis from carcinoma of the breast.

The evolution of some of the specific types of carcinoma of the breast varies. *Paget's disease* of the nipple makes up only slightly more than 2 per cent of all breast carcinomas. It occurs most frequently in women of middle age. Geschickter reported on seventy-two patients in whom the average age was 53 years. The duration of the symptoms averages about three years. The clinical history is usually that of a slowly spreading rosy red dry rash with fine white scales appearing first on the nipple and later spreading to the areola and adjacent skin (Figs. 653 and 654). As the disease progresses the nipple retracts to the level of the areola. Often no definite mass is felt but if present will be directly beneath the nipple. Sometimes the lesion is bilateral. Axillary nodes are involved in about 50 per cent of the cases but they are often clinically intangible.



Fig. 654—Extensive Paget's disease of ten years' duration

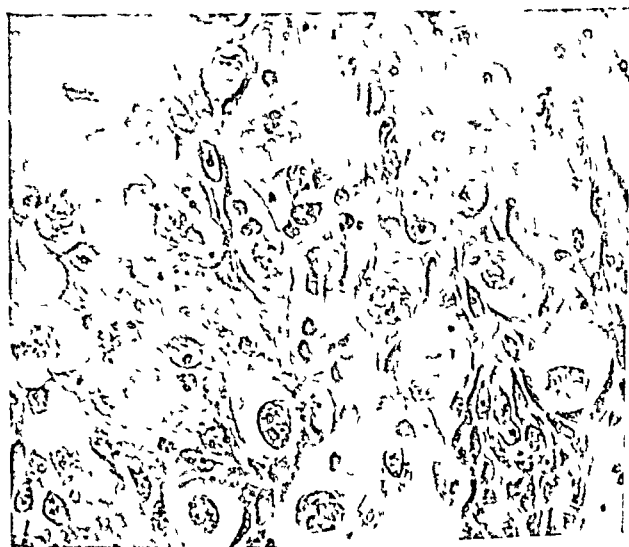


Fig. 655—Photomicrograph showing large so-called Paget cells with clear cytoplasm in the overlying epithelium (high-power enlargement)

time. The secondary type occurs following radical mastectomy. Geschickter reported twenty primary and twenty seven secondary cases, and Taylor reported twenty five primary and thirteen secondary cases. These cases made up less than 4 per cent of all breast carcinomas seen by them. It has a rapid evolution with increase in size of breast. The axillary nodes quickly enlarge, and the skin of the breast becomes edematous and warm. Fever invariably accompanies the tumor.



FIG. 6-3.—Typical lesion of Paget's disease of the nipple.

*Papillary adenocarcinomas* have a closer age range than have the benign tumors. Hart reported on a series of twenty four malignant papillary adenocarcinomas, only one of which occurred in a patient below the age of 35 years. The predominant age incidence was between 40 and 60 years. These tumors are a fairly distinct clinical group. They tend to grow to a large size, are centrally located, often involve skin and ulcerate late but rarely become fixed to the deeper structures. In spite of their large size metastasis to the axillary nodes is surprisingly low.

dissemination of the disease with metastases to viscera. In very infrequent instances, neurologic signs develop and death occurs with symptoms suggesting brain metastases.

Carcinoma of the male breast does not differ in its evolution from that of carcinoma of the female breast except in minor details. In Wainwright's series, carcinoma of the male breast occurred at an average age of 54 years. The tumors have a slower evolution than carcinoma of the female breast, but they are not usually seen until late. By that time the tumor has usually extended to the underlying pectoral fascia and muscle because of the relatively small amount of breast parenchyma. For this same reason, satellite skin nodules and metastases to the axilla are invariably present (Fig. 656). Their terminal course is similar to that of carcinoma of the female breast.

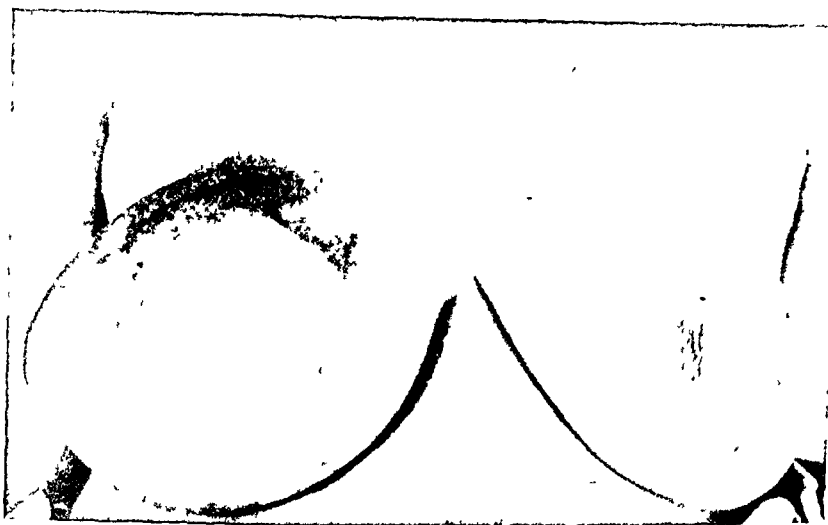


Fig. 657—Typical tendon cystosarcoma phylloides of the breast. Note effacement of nipple without retraction. (From Cooper W. G. and Ackerman L. V. Surg. Gynec. & Obst. 1913.)

The *cystosarcoma* invariably arises in pre-existing fibroadenoma and the clinical history is that of a small, painless nodule in the breast which, after many years of quiescence, suddenly begins to grow. This tumor gradually forms a large mass within the breast, causes very few symptoms except heaviness, and usually remains localized (Fig. 657). The *fibrosarcomas* have a more rapid evolution without any previous story of an existing lump. In the *cystosarcoma* type, ulceration through the skin may eventually take place with resultant hemorrhage and infection. This may cause systemic symptoms with weight loss, anorexia, and symptoms due to anemia. Death comes not from metastases, but from secondary hemorrhage and infection. The *fibrosarcoma* usually develops distant metastases, particularly to the lung, liver, and brain, and, at times, may be widely disseminated. Local recurrence is common in both.

*Mucinous carcinoma* makes up only about 2 per cent of all the breast carcinomas. It commonly occurs near or during the menopause the average age being between 46 and 50 years. These tumors grow very slowly. In Lunge's seventy-five patients, thirty-four months elapsed as an average before fixation of the skin occurred, and ulceration appeared after fifty-eight months. The tumor is smaller than might be expected from the long period of growth. It is found most commonly in the center of the breast or in the upper outer quadrants directly beneath the skin. The overlying fat is atrophied, the nipple protruding and enlarged.

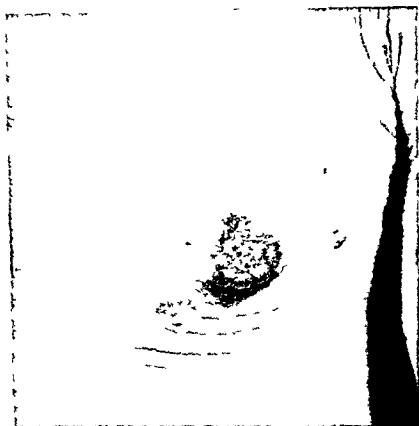


Fig. 6-6—Advanced ulcerating fixed carcinoma of the male breast with satellite skin nodules.

*Lobular carcinoma* of the breast occurs in the younger age groups. These tumors do not form a definite mass for the carcinoma is confined to a lobule early in its evolution. However, late in the disease invasion of the breast parenchyma occurs and the usual clinical picture of carcinoma of the breast appears.

The terminal evolution is the same in all of these tumors. If the tumor metastasizes to the lungs, very frequently pleurisy develops and with further growth hydrothorax appears. Lymphatic metastases to the lungs are not unusual. This type of spread results in considerable dyspnea which may become so severe that the patient becomes bedridden. Cardiorespiratory failure, particularly respiratory, is the most common cause of death from carcinoma of the breast. In a few instances death is caused by cachexia due to widespread



The inspection should include the careful notation of the following

- 1 The symmetry size form and elevation of the breasts
- 2 The presence or absence of traction of the nipple The amount of nipple pigmentation and any signs of scaling or eczematoid lesions Eversion
- 3 Any dimpling or skin attachment overlying the tumor (Such attachments can be seen most clearly when the patient raises her hands over her head) Signs of skin edema

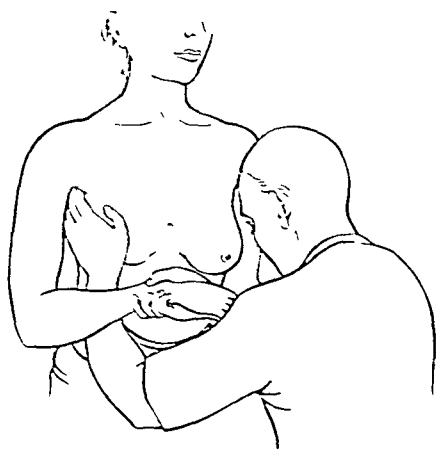


Fig 658

Fig 658—Position of patient for examination of the axilla. The arm is relaxed so that the examiner's hand can explore the entire axilla.

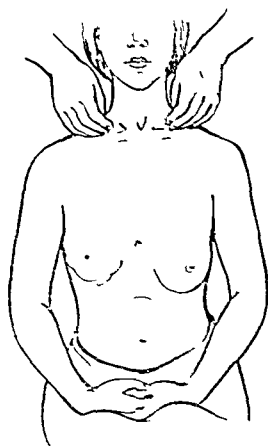


Fig 659

Fig 659—The examining physician should stand behind the patient to examine the supraclavicular lymph node areas.

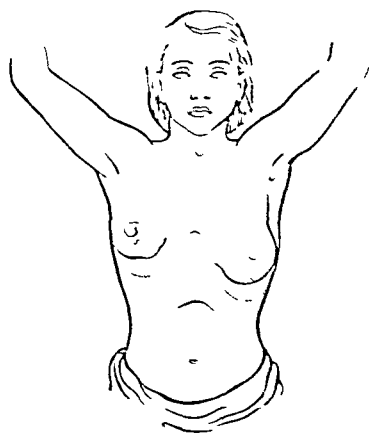


Fig 660

Fig 660—Patient with a carcinoma of the right breast. Raising of the arms demonstrates the relative fixation of the right breast as compared to the left breast.

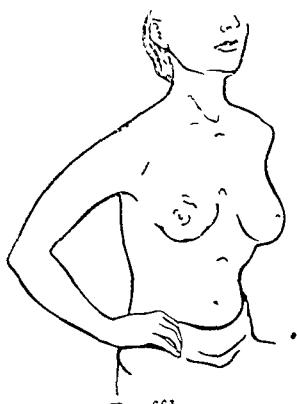


Fig 661

Fig 661—Tensing of the pectoral muscles by pressure on the hips shows fixation of the tumor to pectoral fascia or muscle.

**Follow Up**—A patient who has had a radical mastectomy should be followed indefinitely because local recurrence or distant metastases have been known to make their appearance many years (up to thirty years) after operation (Fig 670). Nathanson showed that a certain percentage of recurrences could be expected in each five year period. Unexplained *weight loss* (ten pounds or more) may indicate spread of the disease to distant organs especially the liver. Dorsolumbar pain in the hips or thighs or signs suggesting arthritis may be related to bone metastases. Dyspnea, pleural pain, or persistent cough are often indications of pulmonary metastases.

However the most important reason for continuing follow up on a patient who has had a radical mastectomy is that the patient has a three to four times greater chance of developing a second carcinoma of the breast than a woman of the same age who is without disease (Kilgore). In 300 mammary cancers studied at the Memorial Hospital fourteen (or 4.7 per cent) of the patients had had the opposite breast removed for carcinoma. This percentage will undoubtedly increase with time (Loote and Stewart). Kilgore in 1921 emphasized the importance of very careful follow up of patients previously treated for carcinoma of the breast. In 659 patients on whom follow up was continued for three years after operation there were thirty seven with bilateral carcinomas of the breast. In thirteen of these thirty seven patients the cancer of the second breast was probably a new neoplasm. Kilgore also pointed out that in three fourths of the cases with new carcinomas the nipple was negative at the time of the first operation.

### Diagnosis

**Clinical Examination**—In the clinical examination of a patient with suspected carcinoma of the breast certain clinical information is absolutely necessary. Some of the questions outlined below are important for the purposes of clinical research.

- 1 Has mammary carcinoma been present in other members of the family?
- 2 If it was present in the mother was the patient breast fed as a baby?
- 3 How many periods of pregnancy and lactation has the patient had and were there any complications?
- 4 Has the patient had any previous breast or pelvic operations?
- 5 Is there any discharge from the nipple? If so of what type?
- 6 Has the patient had any previous trauma or burns of the breast?
- 7 Has the patient had any premenstrual pain and/or swelling of the breasts? If so, how severe?
- 8 What was the date when the first symptom was noticed? What was the date when the first tumor nodule was noted? Was there any pain at that time?
- 9 What was the date of the first visit to a physician? Did the patient undergo any treatment? If so, what were the dates and types of treatment?
- 10 What is the patient's present weight? Has there been any recent loss of weight?

The inspection should include the careful notation of the following

- 1 The symmetry, size, form and elevation of the breasts
- 2 The presence or absence of traction of the nipple The amount of nipple pigmentation, and any signs of scaling or eczematoid lesions Elevation
- 3 Any dimpling or skin attachment overlying the tumor (Such attachments can be seen most clearly when the patient raises her hands over her head) Signs of skin edema

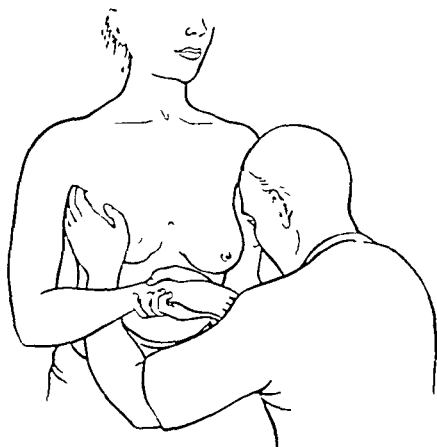


FIG. 658

FIG. 658.—Position of patient for examination of the axilla. The arm is raised so that the examiner's hand can explore the entire axilla.

FIG. 659. The examining physician should stand behind the patient to examine the supraclavicular lymph node areas.

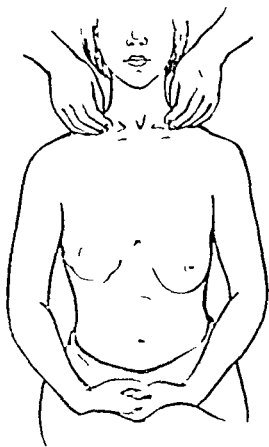


FIG. 659

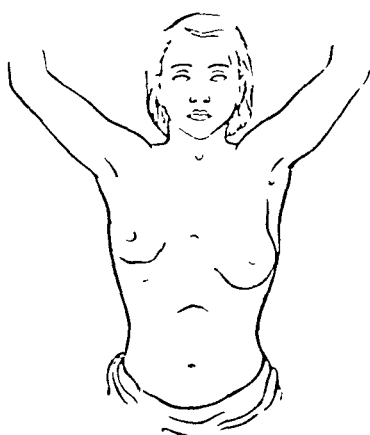


FIG. 660

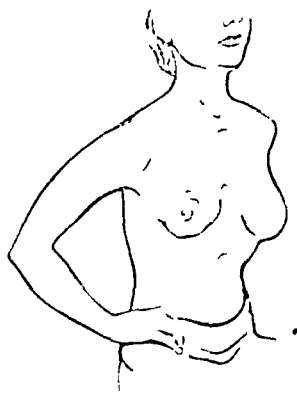


FIG. 661

FIG. 660.—Patient with a cancer of the right breast. The arm is raised so that the examiner's hand can explore the entire axilla.

FIG. 661.—The examining physician should stand behind the patient to examine the supraclavicular lymph node areas.

4 Dilatation of the veins

5 The presence or absence of fixation to the pectoral fascia

The next step in the examination is a careful and *gentle* palpation of the breasts. Rough handling or repeated examinations in inexperienced hands are to be condemned, for dissemination of the tumor is possible with manipulation. Palpation should reveal the following facts:

1 The presence or absence of discharge, fixation, or lack of mobility of the nipple

2 The presence or absence of increased temperature of the skin

3 The mobility of the tumor, the presence or absence of any attachments to the overlying skin, its size in centimeters (three dimensions), whether or not it has well defined outlines and its consistency. A statement should be made as to whether the tumor is apparently cystic or solid.

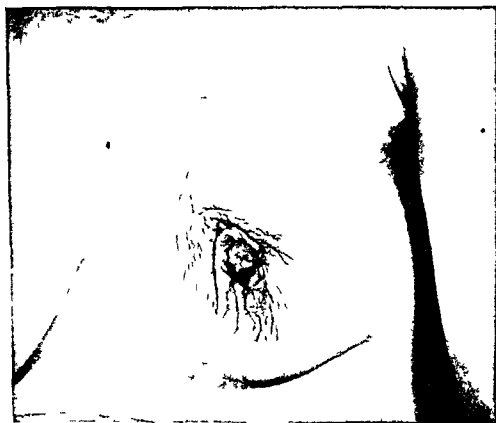


Fig. 66 — Advanced carcinoma of the breast with infiltration of the skin and retraction of the nipple

4. If there are nodes present in the axilla, the number, consistency, fixation to the skin, and measurements in centimeters should be given. *Particular care should be taken to examine the opposite axilla* for the tumor may spread by the afferent lymphatic pathway.

*The presence of a lump in the breast of a woman over 30 years old is a highly significant finding and warrants complete investigation.* A lump is the

first symptom in about 80 per cent of the cases. In about one-third of the cases the lump is painless. When there is pain however it is usually mild, intermittent and only rarely of sufficient intensity or persistence to produce alarm to a physician. The tumor usually feels very hard because it contains a large amount of connective tissue and has indefinite margins which tend to blend with

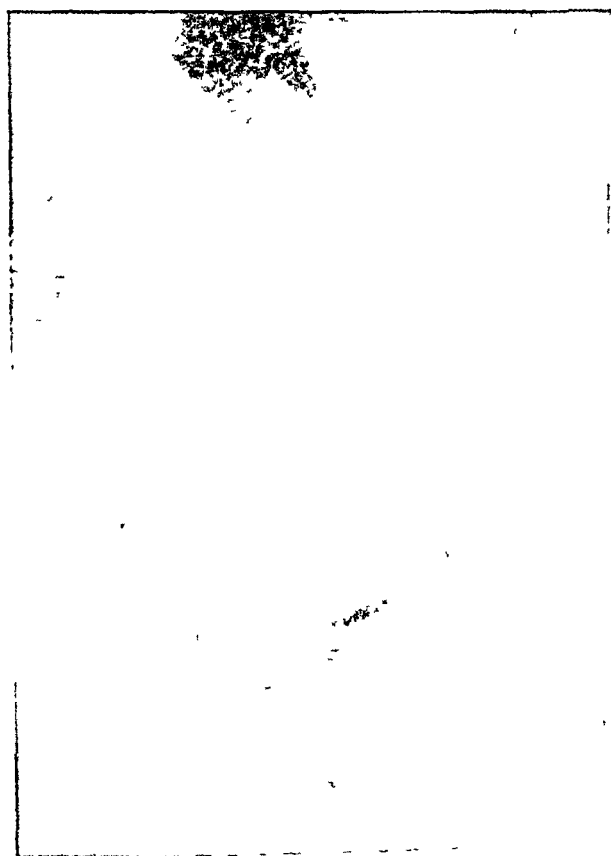


FIG. 1.—Tumor on arm.

the surrounding tissue. In many tumors there is a redness due to the increased vascularity. In some cases the tumor is attached to the skin and if it is on the leg it may be attached to the tibia. The tumor is usually of a firm consistency and is not movable. It is often associated with a large amount of connective tissue and is often associated with a large amount of connective tissue. The tumor is often associated with a large amount of connective tissue and is often associated with a large amount of connective tissue. The tumor is often associated with a large amount of connective tissue and is often associated with a large amount of connective tissue.

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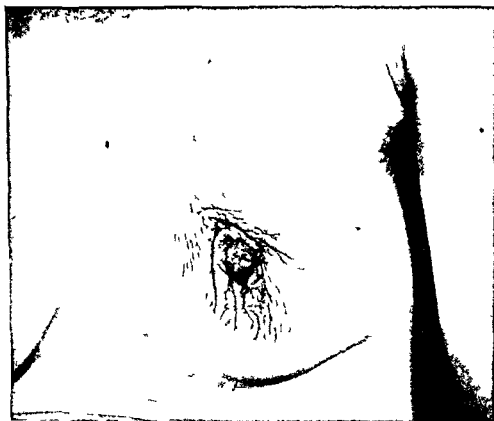


Fig. 66 — Advanced carcinoma of the breast with infiltration of the skin and retraction of the nipple

4. If there are nodes present in the axilla the number, consistency, fixation to the skin and measurements in centimeters should be given. *Particular care should be taken to examine the opposite axilla* for the tumor may spread by the alterolymphatic pathway.

*The presence of a lump in the breast of a woman over 30 years old is a highly significant finding and warrants complete investigation. A lump is the*

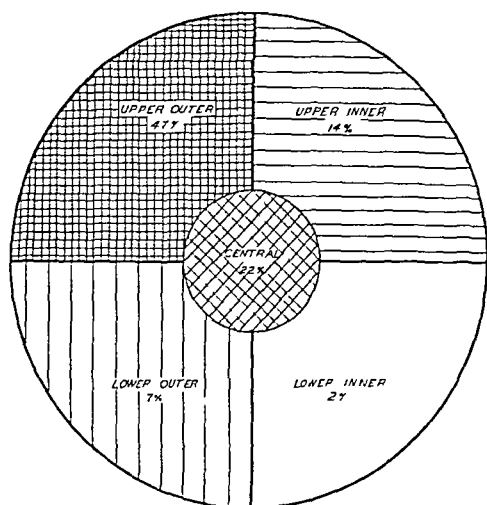


Fig 664 —Diagrammatic sketch of the points of origin of 200 consecutive cases of carcinoma of the breast in patients admitted to the Ellis Fischel State Cancer Hospital

Fig 665 —Retraction of the nipple and periareolar edema with pigskin appearance in carcinoma of the breast.

Carcinomas of the breast are most frequently located in the upper outer quadrant (Fig 664) but can also be located in the other quadrants in the inframammary region, and, at times in the tail of the breast. Very rarely carcinoma can arise in aberrant breast tissue which is most frequently present in the axilla (de Cholnoky).

In advanced carcinoma *skin nodules* may be visible in the region of the tumor over the sternum or even at some distance from the primary lesion but are frequently first noted on gentle palpation, best felt when the patient is lying down. They are usually less than 1 cm in diameter nonulcerated very firm and rose colored and project slightly above the skin level.

*Edema* appears when the dermal lymphatics are plugged with carcinoma. If the tumor is in the central part of the breast the edema usually begins in the areola or just inferior to it (Fig 665). At times it may be seen just beneath the areola secondary to a small carcinoma in the upper outer quadrant. The edematous region has an orange skin or pigskin appearance and has also been likened to saddle leather (Table LX).

TABLE LX CLINICOPATHOLOGIC CORRELATIONS IN CARCINOMA OF BREAST

CLINICAL FINDINGS	PATHOLOGIC FINDINGS
Lump small painless hard	The smaller the cancer the less chance of axillary metastasis hardness directly related to the amount of connective tissue or inflammation present
Attachment to skin	Tumor growing just beneath the skin
Discharge from nipple	If discharge is bloody tumor may have arisen from a pre-existing intraductal papilloma
Prominent veins in region of tumor	Tumor blocking venous return
Edema orange skin appearance to the skin	Tumor growing in subdermal and dermal lymphatics
Fixation to chest wall	Invasion of pectoral fascia and rarely of muscle
Satellite nodules	Extensive dermal and subdermal lymphatic involvement
Hard supraclavicular node	Usually metastasis, rule out benign lesions by biopsy
Contralateral axillary lymph nodes	Usually metastasis, rule out benign lesion by aspiration or formal biopsy
Fixed mass in axilla	Tumor growing in the node breasting through the capsule and growing in the loose fat
Edema of the arm	Tumor blocking lymphatics and venous return
Horner's syndrome (miosis, enophthalmos and narrowing of the palpebral fissure)	Metastatic tumor pressing on or invading cervical sympathetic chain
Diffuse chest pain dyspnea	Tumor involving pleura and probably lung
Circle chest pains (lumbar or scrotic pains)	Questionable metastasis to vertebrae or aortic arch region
Marked extreme weight loss	Invasion of distant metastasis possibly to the liver

It should be emphasized that even after careful examination the clinical evaluation of any mass present in the breast is fraught with difficulty and that even the most experienced physician can diagnose only 70 per cent of the lesions. The rest have to be resolved by exploration frozen section diagnosis or permanent sections. Hospital residents and interns even with superior training, are seldom able to diagnose more than one half of these lesions. The evaluation of axillary lymph nodes is also very difficult and it is remarkable how incorrect